The Canadian Medical Association Journal

JUNE 15, 1958 • VOL. 78, NO. 12

EXPERIMENTS IN MENTAL HOSPITAL ORGANIZATION*

W. S. MACLAY, M.D.,†
London, England

I WANT to spend five minutes reminding you of the structure of the National Health Service in Britain so that the background to my talk is clear, then five minutes telling you about the major recommendations of the Royal Commission's Report on the Law Relating to Mental Illness and Mental Deficiency. Thereafter I shall try to show you that the general principles underlying the Commission's Report are in accord with the general trend of developments in the mental health services and mental hospitals in recent years; this of course is as it should be if there is to be acceptance of a report.

NATIONAL HEALTH SERVICE

The National Health Service in Britain is administered centrally by the Ministry of Health advised by a Central Health Services Council and various committees. There are three main divisions of the Service:

1. Hospital and Specialist Services.
2. Local Authority Services: After-care, maternity and child welfare, midwifery, health visiting, domestic help in sickness, prevention (e.g. vaccination), ambulances, health centres.
3. Practitioner and Dental Services.

So far as the mental health services are concerned, the central authority includes not only the Ministry but also the Board of Control. Most of the functions of the latter have passed to the Ministry excepting those dealing with the liberty of the subject. The change is an important one and I shall refer to it later.

Turning now to the three main divisions:

Hospital and Specialist Services.—The 14 Regional Hospital Boards, which look after regions with populations varying from one to three million, are responsible for all the mental hospitals (147,000 patients) and all the mental deficiency hospitals (60,000 patients) and for the outpatient services.

Local Health Authorities.—They are responsible for the care of the defectives in the community (80,000) and for the prevention of mental illness and for the after-care of those who have been in mental and mental deficiency hospitals. The medical officers of health are becoming increasingly keen on this work, their Society has recently established a psychiatric section, and there is more psychiatry in the syllabus of the course for the D.P.H.

The way in which the work of M.Os.H. has developed is worth considering for a moment. Starting in 1856, their activities for the first 50 years were directed to sanitation and the prevention of epidemics. This was essential because at that time the population had doubled in 50 years (9,000,000 to 18,000,000) and the Industrial Revolution was in full swing. Unbelievable conditions of filth, squalor and misery existed. In 1830 over 30% of children died before the age of five years. Cholera killed 90,000 people in the four famous epidemics between 1831 and 1866; typhoid and typhus raged. In the second 50 years the drive, so far directed to sanitation and environment, was extended by changing it, as has been said, "from the premises to the person"; and so the M.Os.H. took responsibility for the school medical services, maternity and child welfare, T.B. and V.D. services. Social medicine had started. And now in the third 50 years the public health service is becoming actively concerned with man's human relationships in the home, the school and the society in which he lives and works. The M.Os.H. are realizing that mental hygiene is just as vital as environmental and personal hygiene and that it is quickly becoming one of their main responsibilities. There is good reason to hope that in the next 50 years there will be advances in the promotion of mental health and prevention of mental illness just as great as the advances made in other fields of public health in the past.

Practitioner Services.—The practitioners are much more interested than they used to be. Thanks to better education of medical students you get many fewer letters at the psychiatric clinic saying "Seems queer, please see and treat", and many more which show a real appreciation of the psycho-

*A summary of the Academic Lecture given to the First Canadian Mental Hospitals Institute, Toronto, January 22, 1958.

†Senior Commissioner, Board of Control, Ministry of Health, London, England.

Canad. M. A. J.
June 15, 1958, vol. 78

logical aspects of illness. Practitioners have always had to look after the mental health of the patients and families under their care, but now they are applying knowledge to what they handled before by intuition.

THE REPORT OF THE ROYAL COMMISSION ON THE LAW RELATING TO MENTAL ILLNESS AND MENTAL DEFICIENCY

The Commission was appointed in 1954 and presented a unanimous report in May 1957. This has been very well received and the principles are not disputed, though there is much to be discussed about the methods advocated in the report to achieve the desired results. The main recommendations are:

1. To put mentally ill and mentally defective patients as far as possible on the same footing as patients with other forms of illness or disability.

2. To expand the community services including residential services for all groups of mental patients. This involves a great increase in local authority work.

3. To abolish the special designation of hospitals as mental or mental deficiency hospital, thus making any hospital free to accept psychiatric patients on an informal basis even if it is also authorized to accept those who must continue to be subject to compulsory powers. This will give more scope for proper classification.

4. Revision of procedures for admission and discharge and of facilities for review where compulsory powers are used, and the abolition of the present distinction in this respect between mentally ill and defective.

5. Recognition of three main groups of patients (mentally ill, psychopathic and severely subnormal) instead of two (mentally ill and mental defective).

CENTRAL DEPARTMENTS

The process of treating the mentally ill in the same way as the physically ill had been proceeding, so far as central administration is concerned, ever since the functions of the Board of Control, apart from those relating to liberty, were taken over by the Ministry of Health in 1948. It has been a leisurely, unexciting, revolutionary change. In the old days the Board of Control had separate premises and staff and dealt with all aspects of the mental service; its commissioners were expected to be and often were experts in laundries, diets, clothing, farms, etc., as well as being good clinicians and lawyers. The members of the Board remain independent in so far as liberty is concerned, but in all other respects work for the Ministry as specialists in mental health. Now the general work has been passed to the appropriate departments, e.g. outbreaks of infectious diseases are dealt with by the epidemiologists, nursing problems by the nursing division, and so on. It has been fascinating to watch the various officials, medical and lay, gradually stop making their silly little jokes about trick cyclists, hypnotic eyes, etc., and come to accept responsibilities of the mental health service as part of their ordinary duties. I am sure this kind of integration is right, and in this I am supported by as great an authority as Plato, who wrote, "The greatest mistake in the treatment of sickness is that there exist physicians for the body and physicians for the soul and yet the two are one and indivisible". I am sure, too, that the Royal Commission was right to accept the suggestion made by the Board of Control itself that it should commit suicide and be abolished.

OUTPATIENTS

Another way in which the unnatural division between mental and physical illness is being broken down is the acceptance by the general hospitals of psychiatric responsibility. We believe that psychiatric outpatient work should be done in the outpatient departments of general hospitals but that the psychiatrists should come from the mental hospitals, to achieve continuity of treatment and avoid isolation. It is now generally accepted that any all-purpose outpatient department must include facilities for psychiatric O.P. work and that every mental hospital psychiatrist, senior or junior, should spend a considerable amount of time doing community work and not spend all his time in the hospital.

In 1930 there were practically no outpatient departments; now there are nearly 500 for adults, of which less than 100 are at mental hospitals. There are probably enough clinics now and the need is to staff them better and provide better treatment. The unit at St. Thomas's Hospital in London illustrates my meaning. In 1948 there were, in round figures, 600 new patients and 4000 attendances. In 1956 there were 1200 new patients and nearly 14,000 attendances, of which 5000 were for psychotherapy and 9000 for special treatments such as electroconvulsive treatment, methedrine, CO_2 and modified insulin.

ADMISSION WITHOUT LEGAL REQUIREMENTS

Just as psychiatric O.P.D.s are generally accepted, so we are now getting acceptance of the principle that every general hospital should have some psychiatric beds and that *they should be linked with a mental hospital*. There are already between 6000 and 7000 beds for the informal admission of psychiatric patients; these are distributed among special annexes for old people, general hospitals and mental hospitals. The patients are admitted in exactly the same way as ordinary medical or surgical patients. As the law stands at present, mental hospitals designated as such are only

allowed to admit statutory voluntary, temporary and certified patients under the Lunacy and Mental Treatment Acts; and even the voluntary patients, who form over 78% of the admissions, have to sign forms and be reported to the Board of Control. The patients to whom I am now referring are completely outside the scope of the Acts. To achieve this it has been necessary to redesignate parts of mental hospitals so that legally they are no longer regarded as such. Thus another of the Royal Commission's recommendations, namely, that mental patients should wherever possible be admitted in the same way as ordinary patients, is already under way. All the teaching hospitals now have their own inpatient as well as their own outpatient departments, with perhaps two exceptions, one being my own hospital, St. Bartholomew's, which, with a tradition of nearly 850 years behind it, does not believe in accepting new-fangled ideas such as women doctors and psychiatry too rapidly, despite the fact that it received its Royal Warrant from Henry VIII at the same time as Bethlem did.

SIZE OF MENTAL HOSPITALS

You will remember that I stressed that any unit in a general hospital should be linked with a mental hospital. This I believe to be vital; we don't want the kind of mental hospital psychiatrists who work alone in big isolated mental hospitals. As a matter of fact, we don't want big mental hospitals, though we've got them and have got to put up with them, but don't let us build any more. The early mental hospitals in England were not big and were not isolated (e.g. Bethlem, and St. Luke's in London, Bootham Park at York, Cheadle Royal in Cheshire). Hanwell, built in 1831 with 800 beds, was rightly regarded as a monster, and Connolly, its famous medical superintendent, doubted whether he could carry out his policy of humane treatment in it. Dr. Kirkbride, one of the 13 founder-members of the A.P.A., insisted that 200-300 was big enough for a hospital. The 5th Report of the W.H.O. Expert Committee on Mental Health says "the good hospital will be comparatively small"; a recent study for W.H.O. by two psychiatrists and an architect, as yet unpublished, recommends a limit of about 300 patients, with ward units of not more than 30 patients suitably subdivided. Again, this is not new. In 1819 Samuel Tuke ("Practical hints" from a document printed in 1819 concerning the building of Wakefield Asylum) wrote, "In regard to the number of patients who may be allowed to occupy one room, I incline to think that the number ought in no case to exceed fifteen." Again, "I incline to think that the probability of recovery is greater where a moderate number of persons associate together", or again, "When all the evils of large associations are considered it is not perhaps too much to attribute to it in degree the small proportion of cures in some of our larger establishments."

If there is a request for a new 1000 bedded hospital I would urge that there should be two schemes each the equivalent of 500 beds. Then I would distribute the beds like this:

Good O.P., day hospital, and home visiting facilities, means 100 beds not needed. Accommodation, provided either by the Hospital Service or in the community, for old people who though mentally enfeebled do not need or no longer need the facilities of a mental hospital, 100 beds. Short-stay accommodation in general hospitals, 50 beds. Beds for rehabilitation of longer-stay patients, 250 beds. But no one is very sure how many of the long-stay beds are necessary, so let us start with a hundred and add to them as required.

In case you think I am living in fairyland, let me tell you what has been happening. Firstly, in the Manchester Region. There, owing to circumstances which I need not detail, there are some psychiatric units of 100 to 200 beds attached to general hospitals. Each has its own catchment area, from which it admits all types of mental illness, and provides appropriate treatment; each is linked with a big mental hospital to which it was anticipated they would send a stream of patients. To our surprise they are sending only a very small number and seem to be able to deal with their case load without getting silted up. We are inclined to think that this is because the units are small, so patients get individual attention, they are in the centre of the community so they don't lose touch with their friends, there are no vast grounds so they go into the town for their recreation and attend the local cinemas and football matches instead of special hospital ones. It would appear, in fact, that one of the most important trends in psychiatry is a change from a demand for more beds in big isolated hospitals to a demand for more adequate treatment in more suitable surroundings; it is improbable that any further mental hospital beds of the traditional mental hospital type will ever be required, and to me it is certain that the provision of more and more beds is not the way to overcome overcrowding.

TREATMENT IN THE COMMUNITY

Now let me tell you about another interesting experiment being carried out at Graylingwell Hospital in the South of England. For years we have been praising hospitals for increasing their turnover; admissions have jumped from 55,856 in 1950 to 88,542 in 1956, length of stay has shortened, 78.5% of the admissions are voluntary, more in the good hospitals. Recently we have come to think that it is time to encourage hospitals to cut down their admission rate so long as they are able, as we think they should be, to provide adequate treatment in the community. At Graylingwell the admission rate was 735 in 1950, while for 1956 it was 1347, an increase of 82.3%. The increase of the admission rate looked as though it

would continue indefinitely, and it was decided to try an experiment to see if expanded facilities for outpatient, day hospital and domiciliary treatment could materially affect the great annual increase of admissions to the mental hospital. The experiment was backed by the Nuffield Provincial Hospitals Trust and is going on now. The area served by this pilot experiment is one with a population of 160,000 people. The effect of the experiment is checked by comparison with what happened in this area in 1956, and by comparison with another area of the same size which also admits patients to Graylingwell.

The headquarters of the experiment provide accommodation for an outpatient department, a day hospital and a domiciliary service.

The results have been startling.

Admissions to Graylingwell Hospital	*1956*	*1957*
Admissions from catchment area not served by the new service	651	679
Admissions from catchment area served by the new service . . .	601	257

i.e.—A reduction of the admissions by 57.2%.

A point of considerable interest is that not only was the impact of the service felt on the recent, short-stay type of recoverable patient, but also on the admission of the more advanced and acutely mentally ill patient upon whom much effect was not expected. Among these there has been a 40% reduction.

The effect of this service on the admissions of old patients, i.e. patients over 65, is also important when it is remembered that national statistics show that 20% of those admitted and 30% of mental hospital residents are over that age. Here the effect is most apparent in the 65-75 age group, but among the whole group of 65 years and over there was a reduction from 186 to 107, i.e. 42.5% reduction.

GERIATRICS

In the Oxford Region, Dr. Cosin at the Cowley Road Geriatric Hospital has been an active developer of new ideas about geriatrics. So far as the effect of his work on the mental hospitals is concerned, the Senior Administration Officer writes in his annual report, "The link now formed with acute geriatric units has been of great advantage. The proportion of patients admitted over the age of 65 to mental hospitals in this region was until recently as high as 25% of all admissions. It has been shown that this can be reduced to 10% or even lower by admitting patients to a geriatric unit and sending to a mental hospital under certificate only those with violent or difficult behaviour." This is not another service being removed from the mental hospital; it is a joint enterprise with the psychiatrist from the mental hospital attending the geriatric unit regularly.

Everything must be done to avoid the common idea that once an old person goes to hospital all hope has gone and the relations are absolved of responsibility. A follow-up of patients in three hospitals showed 40% discharged after two years, most of them in the first year.

At Mapperley Hospital in Nottingham elderly patients are always seen before admission and then, if there is any expectation of prolonged mental hospital care not being needed, the relatives are given a fixed date, usually about a month or six weeks ahead, on which to take the patient home. The patient hears this being done, so neither patient nor relative gives up hope.

The medical superintendent of Mapperley Mental Hospital has achieved such excellent cooperation between the local authority and regional hospital board services that it can be said with truth that a state of complete integration into a single mental health service has been achieved. This integrated service has been described by Dr. D. MacMillan (*Lancet*, 2: 1094, 1956).

DAY HOSPITALS

I am not going to talk about day hospitals; after all, one of the first was started here in Canada. Unfortunately, the term "day hospital" is as uninformative as terms like "psychopath" or "group treatment". If they are to make sense they must be defined when they are used. There are now about 20 day hospitals in England, and no attempt has been made to create a uniform type.

STAFF

All these activities, additional but related to inpatient services, need more staff and the staff must be well trained if they are to be effective. In England there has been an increase of more than 50% in the number of psychiatric consultants in the National Health Service since 1949 and more are needed. It is essential that there should be a good supply of well-trained psychiatrists to follow on. It is the duty of the departments of psychiatry in the universities and the psychiatric teaching organizations to see to this, and they need constant support in their efforts to develop an interest and enthusiasm for psychiatry in both undergraduates and graduates. This means that good teaching and research work on inpatients and outpatients must be carried on in the same way as they are in other branches of medicine and must be just as available to students.

INPATIENTS

Now it is time to say something about the patients who go into hospitals. They fall into two groups, the short-stay and the long-stay. I don't want to say much about the short-stay cases, by which I mean a stay of under a year. I choose a year because over 90% of all patients who are

discharged are discharged within a year. I think too many are being admitted, but the increased demand is striking and indicates that there is a real need for beds for short-stay patients, and that there is a marked loss of fear of mental hospitals and a growing appreciation of the treatment that they can give. In 1946 there were approximately 36,000 admissions, of which 18,000 (50%) were voluntary. In 1956 there were 88,542 admissions, of which 69,479 (78.5%) were voluntary. More than 55% of those admitted were discharged within three months and over 70% within six months. A combination of spontaneous recovery and good results from early treatment ensures interest and a sense of encouragement regarding these patients.

What about the long-stay cases? Although the percentage of admissions left after death and discharge at the end of a year is comparatively small, it accumulates and occupies more than 80% of the accommodation. What is being done about them? It is interesting that something seems to be happening, because in Canada and New York, as in my country, the number of those in residence is beginning to fall.

PERSONS UNDER CARE IN ENGLAND AND WALES

Year	*No. of patients*	*Increase or decrease*	
1949	147,288		
1952	149,353	plus 2065	
1953	151,378	" 2025	
1954	152,144	" 766	
1955	150,856	minus 1288	(Redesignation = 649)
1956	149,480	" 1376	(Redesignation = 308)

I believe that the reduction follows an increasing appreciation that many of the long-stay patients have become chronic, not because of their illness but because of the kind of hospital regimen in which they have been forced to live. This need not be unkind; a kindly taking-over of all responsibility from the patient can be just as destructive to his personality as cruelty or neglect. It has become clear that the group of chronic patients is not the static mass of unmodifiable and antisocial humanity it was thought to be. In England the physical methods of treatment such as E.C.T., insulin and leukotomy, and the tranquillizing drugs (which can be such a menace outside the hospital and such a blessing in it) have made many patients more accessible and more able to react to methods of rehabilitation, and so there is a steadily growing interest in the effect of the therapeutic community, group treatment, the open hospital, industrial schemes, etc., on the chronic population of mental hospitals.

THERAPEUTIC COMMUNITY

Let me say something in the first place about the so-called "therapeutic community", and start by quoting Rapaport (*Human Relations*, Vol. 9, No. 9):

"This term has come into vogue among those who seek to create a social milieu which is in itself therapeutic and which can also be beneficial as an integral part of other forms of treatment. Research by sociologists and psychiatrists in this field has brought to light factors that hinder effective utilization of the social environment for therapy; such factors are the wasted energies of informal ward interaction, the social barriers between patients and staff in the treatment situation, disturbing effects of hidden staff disagreements, personal barriers to liberalizing hospital staff attitudes."

A therapeutic community which has had a big influence on current mental hospital organization in England is that of Dr. Maxwell Jones at Belmont. This was originally set up in 1947 to study what could be done for neurotics with special difficulties with regard to employment. It soon became apparent that most of the patients had personality problems and corresponded closely to what is usually meant by psychopaths; frequently they had histories of long periods of unemployment and antisocial behaviour, with, perhaps, criminal records. Both psychiatrists and Labour Exchange officials have in the past felt hopeless about this problem group. Strict attention to the social milieu within the hospital, special group techniques, co-operation with the Ministry of Labour Training Centre nearby and testing in real-life situations in various employments provided by over 30 co-operative local employers have led to surprisingly good results. A follow-up of about 100 patients 6-9 months after discharge showed that 53% had worked full time since leaving, and 67% had made a fair adjustment. In treating these personality problems the importance of the family had become more and more apparent, and family group meetings are now held in the unit to bring other members of the family into the treatment situation. I have no time to talk about the methods used, but the work of a research team on the therapeutic community at Belmont over the last three years will soon be published and a long-term follow-up is being carried out.

Many big mental hospitals have been studying how to make their hospitals more effective as therapeutic communities. Netherne Hospital has, perhaps, given more thoughtful study to it than most, with the result that a variety of changes have been made and a variety of experiments tried. One of the first principles has been acceptance of the need to have the enthusiastic co-operation of the staff, and a lot of thought has been given to the problem of communication between different strata of staff, so that all might understand the purpose of any change.

One experiment has been the splitting of a large ward of 150 of the most deteriorated patients into three groups, each of which was moved into a smaller ward so that the population of each of the three was fifty. The staff of each consisted

of a head nurse, two nurses and a ward orderly. After a difficult initial period of rejection and hostility the experiment got under way. I cannot here describe the routine of habit-training that was developed, but within three months it was found possible to train a group of 50 to quite a different standard of living. At first 33 patients were incontinent, now only one is. Of the original 50, only 4 were at all occupiable, now 17 do regular ward work, 17 attend occupational therapy and only 16 are not usefully occupied. They look healthier and less slovenly; they have put on an average of 14 lb. in weight. Their table manners are markedly better, they do not quarrel and they are much calmer.

Dr. Monro at Long Grove Hospital when he starts a change always puts into the unit where it is to be tried patients from wards all over the hospital, so that when they go back they will talk about it to staff and other patients. He reckons that it takes about four years of careful propaganda in a hospital before major changes can be attempted.

More recently another experiment has been tried at Netherne. It was observed that social instincts, however dormant, became observable at social events when the sexes were mixed. Women who were aggressive and obscene before a social event in a male ward became co-operative with the nurses when the actual event took place. On return to a ward after a social gathering there was nearly always a relaxed atmosphere and they all settled down quickly and went quietly to bed. It seemed possible that if given opportunity to meet and mix with the opposite sex the men and women should, if their behaviour at socials was any indication, benefit in many ways, and so the experiment was started.

Two villas side by side were used each for 43 of the most deteriorated patients in the hospital. Apart from sleeping arrangements, the sexes mix freely for work, meals and recreation. After six months the following noticeable changes for the better have been noted:

1. Increased sense of responsibility.
2. Greater attention to toilet and appearance.
3. More male patients shaving themselves, shorter time needed for dressing.
4. Increased spontaneity, e.g. asking for help when feeling depressed.

The staff had more difficulty in adjusting to the change than the patients and a weekly ward meeting was essential as a safety valve. At this meeting the staff express complaints, pool resources, reassure each other and bolster each other's morale.

INDUSTRIAL WORK FOR REHABILITATING CHRONIC PATIENTS

The importance of regular useful work in preventing deterioration has long been known and so has the converse, viz. that an inactive regimen can aggravate, if it does not actually cause, the condition of the patient. In 1801 Pinel wrote: "It is noteworthy that silence and tranquillity prevailed in the Asylum of Bicêtre when nearly all the patients were supplied by the tradesmen of Paris with employments which fixed their attention and allured them to exertion by the prospect of a trifling gain." Despite the recognition of this, there has been a tendency for occupational therapy to become divorced from real work. Between 1949 and 1954 members of the M.R.C. Social Psychiatry Research Unit showed that both high-grade and low-grade mental defectives could be trained to perform simple industrial tasks and that if these patients were employed on practical work, for which they could earn money, their social recovery was accelerated. This work was carried out at the Manor Hospital, near London. The unit then transferred its activities to Banstead Mental Hospital, where they have shown that patients, long considered to be unemployable, can carry out simple industrial work and earn money. It is of interest that the best incentives are money and social prestige and that the most difficult group of patients are the chronic schizophrenics, especially the paranoid group, who showed themselves relatively impervious to both financial and social incentives. Dr. Carstairs, director of the unit, compares them to shy children who refuse the advances of over-demonstrative adults but soon regain confidence if not made the centre of attention. He considers that it is not the reward which these patients reject so much as the disturbing experience of an unfamiliar person engaging them in an interpersonal relationship.

Industrial schemes employing long-stay patients on remunerative work have started in about a dozen other mental hospitals, notably Cheadle Royal and Fulbourn; the greatest difficulty is the provision of suitable industrial work, even in a time of full employment.

A further development of the principle of enabling suitable patients to work in factory-like conditions has been achieved with the help of the Ministry of Labour and National Service, who have made it possible for suitable patients to work in their Industrial Rehabilitation Units. The I.R.U.s are intended to bridge the gap between the hospital and the factory, and they have taken work therapy further than has been attempted before on a large scale. They are available to people handicapped either physically or mentally. The moment a patient enters an I.R.U. he leaves the protective atmosphere of a hospital and feels himself back in a working environment; to quote from an article describing this:

"It is the sense of purpose behind the tasks in the workshops, and the fact that working hours are spent in an authentic industrial atmosphere (complete with clock-punching) that do most to restore the ex-patient's confidence in himself. When he has successfully faced

industrial conditions in the I.R.U. he knows that he can face industrial conditions outside; and the physical as well as the mental condition of many patients improves rapidly the moment this truth dawns on them."

Up to the end of 1955 over 200 patients from 29 mental and mental deficiency hospitals had attended; 81 were neurotic, 75 psychotic and 52 mentally deficient. The results of the scheme indicate that mental and mentally deficient patients have almost as good prospects of satisfactory resettlement as have the other patients who attend the I.R.U.s mostly for medical and surgical conditions.

FREEDOM

As a natural corollary to the methods of treatment and rehabilitation to which I have been referring, it has become possible to give to patients much more freedom than could have been thought of some years ago. A survey of the 106 big mental hospitals which contain 95% of the statutory patients in England and Wales showed that they contained a total of 2684 separate ward units (i.e. day and night space) and that two-thirds (1785) were unlocked by day and only one-third (899) locked. Twenty-three hospitals have less than four locked ward units, including eight hospitals with none. These eight are not all in one part of England but are scattered all round it. I myself am as yet not sure whether it is wise to try to open every ward, but I am sure that it is good to open all except one, or possibly two, on each side of the hospital. One vital principle of the open hospital is that the staff must support and approve of all changes made; they must be continually stimulated and supported, for if doors are to be opened the mental hospital must be a happy and confident place. Patients must be happily occupied and their occupations should be outside the wards, which should be used mainly for eating and sleeping. Recreations too must be provided away from the wards. The patient must be respected as a person. His complaints and requests and those of his relatives must be given due consideration. Clothing must be good. Holidays and visiting must be encouraged. Even the hostility of the paranoid patient can be worn down by constant kindness. Why should a patient leave the only place where he can always be sure of a kind word and a sympathetic ear?

I would like to quote from two articles about open hospitals. Firstly, from an article by the chief male nurse of De la Pole Hospital, near Hull: he writes:

"I have attempted to describe how we cleared the airing courts and exercise grounds and instituted group therapy for rehabilitation of chronic patients. One by one we removed the freedom-thwarting, morale-depressing spring locks from every ward door. With the absence of these clanging, self-retaining door catches, a new atmosphere pervaded these hitherto constantly locked wards. Everything and everyone within them appears to have brightened up. A strange, relaxed peacefulness has taken over from the harsh, militant, prison-like surroundings which dominated the old asylum routine."

Secondly, from an article by Dr. Bell, who was a pioneer of the open hospital in Scotland. In it he mentions the effect of the open hospital on visitors. He quotes from the nurses' notes:

"After four years of the open door system we, the members of the nursing staff, note a great change in the attitude of patients' relatives. They now appear to regard us as the patients' friends, whereas in the old days most visitors regarded us with considerable disrespect. We think the reason was that the nursing staff had to escort them along the corridors, locking every door behind them. In those days we were more or less looked on as jailers. The new approach is very welcome to us."

Perhaps at last we are reaching the day when we can remember without an uneasy pricking of conscience Florence Nightingale's statement that "The first requirement of a hospital is to do the sick no harm", or more recently, the late Dr. Kraus's view expressed in a W.H.O. memorandum that "bad mental hospitals are worse than no mental hospitals".

TRENDS

What then is going on in British psychiatry?

1. Mentally ill and mentally defective patients are as far as possible being put on the same footing as patients with other forms of illness or disability. The increasing outpatient and inpatient facilities at general hospitals are evidence of this; so too is the increase in the number of voluntary patients admitted to mental hospitals and the development of units at them to which patients can be admitted informally in exactly the same way as to general hospitals.

2. The realization that mental hygiene and early treatment in the community can promote good health, prevent or arrest illness and in many instances avoid the need for admission to hospital.

3. The realization that the community can care for many mentally ill and defective patients who are at present isolated in special hospitals and institutions. These patients can, with proper incentives and rehabilitation, support or partly support themselves, instead of being a constant drain on national resources, with benefit both to the individual and to the community.

4. The realization that big hospitals are apt to be bad hospitals and can be potent factors in the creation of chronic patients.

5. The realization of the importance of a therapeutic community and of active rehabilitation

Canad. M. A. J.
June 15, 1958, vol. 78

methods, and that the way in which these can be developed can be studied scientifically by suitably trained persons.

6. In the field of mental deficiency the extension of vocational training methods, better supervision of defectives in the community, extension of day-hospital facilities and more intensive habit training will result in more defectives being cared for in the community and an increased proportion of low-grade patients in the hospitals.

Finally, I would like to express a strongly felt belief that central dictation, however tempting and however sound, must be kept down to a minimum in order to ensure that a sense of responsibility for progress is preserved among those who do the actual work.

Experiments in all fields of psychiatry must continue and can continue with safety so long as those concerned remember and agree with the wisdom of Seneca, when he wrote *Res sacra miser*—"A sick person is sacred."

RÉSUMÉ

Les tendances actuelles qui se dégagent de l'état de transition par lequel passe la psychiatrie anglaise sous le Service de la santé nationale peuvent se résumer comme suit:

Les malades mentaux et les arriérés sont autant que possible considérés sur le même pied que les malades souffrant d'autres forms d'affection ou d'infirmité. L'amplification des facilités des dispensaires et des salles d'hôpitaux généraux en témoigent, de même, l'augmentation du nombre des patients volontairement admis dans les hôpitaux psychiatriques, ainsi que le développement dans ces institutions d'unités où l'on peut admettre des malades sans plus de formalités que dans les hôpitaux généraux.

Les autorités se rendent compte que les mesures d'hygiène mentale ainsi que l'application d'un traitement précoce au sein de la communauté conservent la santé, préviennent les maladies ou les enraient dès leur début, et dans plusieurs cas, évitent le besoin d'hospitaliser le malade. Elles se sont aussi rendu compte que la communauté peut se charger de plusieurs malades mentaux et arriérés qui sont actuellement casés dans des institutions et des hôpitaux spécialisés. Ces malades avec de l'encouragement et de la réadaptation peuvent subvenir à leur propres besoins, entièrement ou en partie, au lieu d'être à charge à la société de sorte que l'individu lui-même et la communauté y gagnent de part et d'autre.

On a enfin compris que les très grands hôpitaux risquent de n'être pas de très bons hôpitaux; qu'ils contribuent beaucoup à rendre chroniques les malades qui y stagnent. On reconnaît l'importance du milieu thérapeutique que peut offrir l'hôpital et des méthodes de réhabilitation active dont l'évolution est à même d'être étudiée par des personnes préparées à cet effet. Dans l'arriération mentale, une meilleure orientation selon les aptitudes, une plus grande surveillance des simples d'esprit dans la communauté, un emploi plus complet des services qu'offre l'hôpital pendant la journée, ainsi qu'une formation plus poussée des habitudes, permettront à de nombreux arriérés de subsister dans la communauté et augmenteront la proportion des petits mentaux dans les hôpitaux.

On doit résister aux tentations qu'offre la centralisation dans ce domaine afin de ne pas dépouiller ceux qui, en fait, accomplissent le travail, de leur sens des responsabilités.

A FOLLOW-UP STUDY AFTER THOROTRAST CAROTID ARTERIOGRAPHY*

A. BERRETT, M.D. and
D. L. McRAE, M.D., *Montreal*

THOROTRAST, a 24% colloidal suspension of thorium dioxide, was first used as a contrast medium for cerebral arteriography by Egas Moniz in 1931. It soon became extensively employed as a contrast medium for demonstration of the liver and spleen as well as the blood vessels. Thorotrast produces excellent contrast because of the high atomic weight (232) and high atomic number (90) of the thorium in it. There seem to have been fewer allergic reactions with it than with organic iodine preparations. Over 200 articles have appeared on it and a controversy has arisen with regard to its toxic effects. Much of the criticism is due to the fact that several independent workers have demonstrated a carcinogenic effect in animals. Thorium is radioactive.[13-15, 19] It has an extremely long half-life of 1.65×10^{10} years and it is poorly excreted by the body. Should it be deposited outside the blood vessels, it produces granulomatous sclerotic reactions at the site of injection. It has been used less in recent years for these reasons.[3, 4, 6, 16, 18, 21, 22]

Because of the extremely long half-life of thorium and also because only about 10% is excreted by the body after intravascular injection, thorotrast is useful for the study of long-term effects of small quantities of internally deposited radioactive material. Such study will lead to better appreciation of the late effects of radioactive elements in the body. Many of the problems are complex, controversial and incompletely understood, and large series are essential for more adequate evaluation of the problems. As yet little information is available concerning the late effects of thorotrast in man.

The effects of thorotrast in man depend on three of its properties, radioactivity, particles of thorium dioxide and the chemicals used for suspending and stabilizing the colloidal particles of thorium dioxide.

When thorotrast is injected into the blood stream, some 90% of the thorium dioxide is rapidly taken up by the reticulo-endothelial cells of the spleen, liver, bone marrow and certain lymphatic glands. The other 10% is excreted through the kidneys during the first 48 hours.[8, 9] The 90% that is taken up is retained almost indefinitely in the body. A point

*From the Department of Radiology, Montreal Neurological Institute, McGill University.
This project was assisted by a grant from the James Picker Foundation for Radiological Research.

Growth of total activity of Thorium + decay products starting with pure TH^{232}.

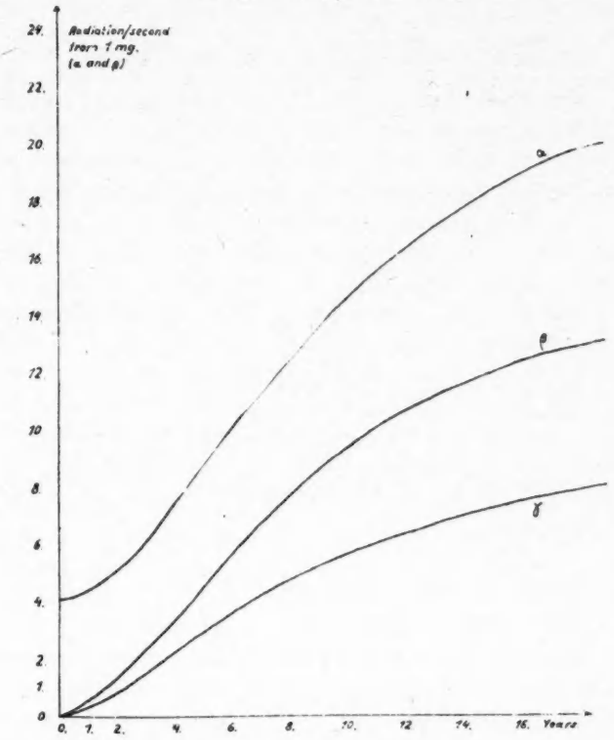


Fig. 1.—Build-up of radioactivity of thorium and its decay products (Finsen Institute).

of fundamental importance is the fact that with the decay of thorium in the body there is a build-up of radioactivity which takes about 20 years to reach a maximum (Fig. 1).

Thorium itself produces only alpha rays but its decay products produce beta as well as gamma rays. Ninety per cent of the radiation produced by thorium and its decay products consists of alpha particles. These have a range of only 40-80 millimicrons in tissue and therefore act almost entirely intracellularly. Nine per cent of the radiation produced by thorium and its decay products is in the form of beta rays with a range of less than 1 cm. in flesh which are almost completely absorbed in the body.[8] Only 1% of the radiation is due to gamma rays which may be picked up by external radiation detectors. High radiation counts may be obtained over the liver and spleen as well as at sites of extravasation.

In one of our patients Dr. L. Stephens-Newsham scanned the whole body with a scintillation detector for possible localized radioactivity. Over the liver the amount of radioactivity was about 50% above the background level but the activity over the spleen was equal to background. No other area of the body showed increased activity. More recently four other patients were examined by the whole body profile counter[5] as modified at the Royal Victoria Hospital. This is a scintillation detector with a crystal 3 inches in diameter which counts successive whole widths of the body as it passes along the length of the body. In two cases a small peak was demonstrated in the neck region apparently due to extravasation of thorotrast at the time of arteriography. In all cases a large peak at the level of liver and spleen was found. No other areas of abnormal radioactivity were found.

The fine particles of thorium dioxide measure 3-10 millimicrons in diameter and may act as tiny foreign bodies when deposited interstitially and may play a part in the formation of thorotrastomas.

It is possible that the chemicals used for suspending and stabilizing the colloidal particles of thorium dioxide are local irritants.

LATE COMPLICATIONS OF THOROTRAST INJECTION

Extravasation at the Site of the Injection with Subsequent Fibrotic Manifestations[11]

Where there is accidental deposition or extravasation into the soft tissues a granuloma results. The tissues become involved in a hard fibrous reaction spoken of as a thorotrastoma. Neoplastic transformations seem to be rare in thorotrastomas, however. Months or years after the carotid injection a lump in the neck is discovered by the patient or his doctor. The patient's disability will vary and will depend partly on the amount of extravasation and partly on the structures that are involved. There may be no symptoms, the mass being discovered by accident. Occasionally thorotrastomas in the neck may be responsible for severe disability to the patient because the surrounding nerves become involved in the constrictive fibrotic process. A variety of symptoms have been reported, including dysphagia, dyspnœa and hoarseness. Patients with recurrent laryngeal paralysis, particularly if it is bilateral, may develop œdema of the larynx in the presence of a respiratory infection. The resultant respiratory difficulty may require tracheotomy. Dense deposits are seen in radiographs of the neck (Fig. 2). On histological examination they are found to be made up of thorium dioxide particles, calcium and occasionally even small islands of bone. The diagnosis may be confirmed by means of a gamma ray detector which may show high activity over the granuloma. Treatment is surgical excision but should be reserved for cases with troublesome symptoms since the diffuse fibrotic reaction makes the operative procedure extremely difficult.

Possible Carcinogenic or other Malignant Sequelæ Occurring either at the Site of Injection or in the Liver[12, 13, 15, 16]

The few cases of malignant sequelæ that have been reported are difficult to evaluate. Some of the liver neoplasms were rapidly proliferating but they did not metastasize. They are regarded as malignant by some pathologists and as benign by others. In general the liver tumours are difficult to diagnose and no dogmatic conclusions can be drawn from the small number available. Fibrosis of the spleen is mentioned by some authors as a

Canad. M. A. J.
June 15, 1958, vol. 78

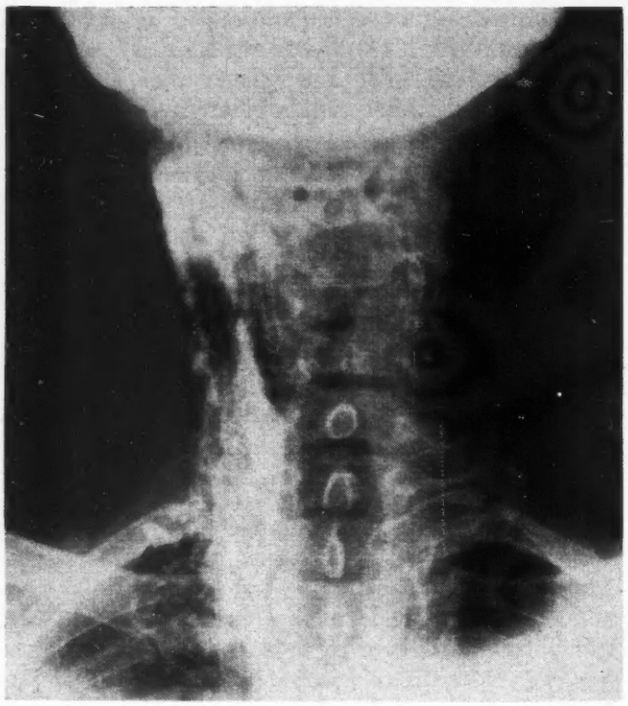


Fig. 2.—Right-sided thorotrastoma 11 years after extravascular injection of 10 c.c. of thorotrast.

late complication of thorotrast injection but no malignancies of the spleen have been reported. We could find no reports of sarcoma of the soft tissues at the site of injection.

Hæmatological Sequelæ[1, 8, 10]

Slight changes in the peripheral blood counts in the course of exposure to ionizing radiation are difficult to evaluate for a number of reasons. They may represent physiological variations, statistical variations, technical errors or changes due to the disease for which radiation is being given. In thorium-contaminated patients the picture may be further complicated by primary intracerebral disease and by anti-epileptic drugs.

The erythrocytes are not significantly affected by thorium dioxide. Backer[1] examined the peripheral blood in 131 thorium-contaminated patients and found a leukopenia in 24% of the patients on the first blood count. At succeeding examinations, however, the great majority were found to have normal blood counts. There was a lymphopenia in 39 of his patients at the first count. A second blood count showed a normal number of lymphocytes in 62% of these. He concluded that blood counts are a poor indicator of radiation damage in the low dosage range. Most hæmatological sequelæ reported have been minimal and equivocal.

In our series there was no significant leukopenia. One patient showed a lymphocyte count of 14% and a second of 12%, 15% being taken as the lowest normal value.

A few isolated cases of more severe blood diseases have been reported. These include aplastic anæmia and leukæmias. Whether or not these were sporadic examples or whether they were due to thorotrast is difficult to determine.

Montreal Neurological Institute Patients

We studied 136 patients who had had thorotrast arteriograms at the Montreal Neurological Institute between 1934 and 1950. The average length of follow-up has been 12½ years with a minimum of five years and a maximum of 22 years. Either unilateral or bilateral carotid arteriography had been performed using an average of 25 c.c. of thorotrast per examination. The injections were made after exposure of the carotid artery in the large majority of cases. Circular letters were sent to the patient or to the next-of-kin as well as to the patient's home physician. We were able to obtain a satisfactory follow-up on 134 of the 136 patients, 68 of whom were alive and 66 of whom were dead.

Analysis of the Cause of Death in the 66 Patients now Dead

Two patients died shortly after arteriography. The first died about 12 hours after arteriography during which both right and left carotid vessels were exposed and injected under direct vision. She had some respiratory difficulty after the procedure and tracheotomy was performed even though there were no objective signs of tracheal compression. At autopsy there was some hæmorrhage and œdema around the trachea and the other structures of the neck but it was thought by both the pathologist and the surgeon to be no more than the expected amount. The cause of death was obscure. Although we do not regard this as a thorotrast death, the operations no doubt were at least partly responsible. The cause of the hæmorrhage is of some interest. Johansen[9] states that this tendency to hæmorrhage may be due to a fibrinogenopenia which results from a combination of thorium and fibrinogen. This transient fibrinogenopenia may be responsible for certain cases which show an early tendency to hæmorrhage. When the take-up of thorium by the reticulo-endothelial system has been concluded, the amount of fibrinogen in the blood rises again. This tendency to excessive hæmorrhage was also noted by McMillan[17] in rats. The control of hæmorrhage after thorotrast injection may be a troublesome feature. One other of our patients continued to ooze blood from both incisions after bilateral carotid arteriography. This necessitated re-operation under general anæsthesia. The second patient died a few hours after the carotid arteriogram. At postmortem examination he was found to have a large right-sided glioblastoma multiforme as well as ipsilateral cerebral softening. There was insignificant hæmorrhage about the incision over the right carotid artery.

Fifty-one patients died of the disease that led to the carotid arteriography. Almost 85% of these patients died within the first five years, usually

within the first two years. Most of them had had subarachnoid or intracerebral hæmorrhages or brain tumours. In these patients the primary cause of death given on the death certificate or the hospital chart was intracranial hæmorrhage or brain tumour. In none was there any suggestion of leukæmia, aplastic anæmia or malignant tumour of the liver or spleen. Ten patients died of accidents and other unrelated conditions following discharge from the Montreal Neurological Institute.

Three patients died of malignant disease other than brain tumour. One died of carcinoma of the stomach. A second had an epidermoid carcinoma of the floor of the mouth which metastasized to the neck, lungs and pleura. The third had an inoperable carcinoma of the right lung. Histological examination showed an undifferentiated small-cell bronchogenic carcinoma. These three cases represent diverse forms of carcinoma that might be found in any sample of the population. Three cases of malignant tumour is no greater incidence than would be found in a population of similar age and sex followed for an equal period.

Analysis of Living Patients

Of the 68 patients still alive we could reach 26 for more detailed study. We assessed the general health of these 26 patients by taking personal histories and in addition by obtaining histories from their family doctors. We studied the distribution of thorotrast by radiographs of the neck, chest, abdomen and one lower limb. Hæmograms were performed on all 26 patients.

The Finsen group[8] of workers found no characteristic syndrome in their patients. The symptoms listed were generally vague, non-specific, and difficult to assess. We experienced difficulty in confirming even these observations. It is important to keep in mind that practically all of these patients originally came to the Neurological Institute with some serious disease for investigation. It thus is difficult to assess vague symptoms such as tiredness and weakness. Some of the patients were still seriously disabled by the original intracranial lesion. Another factor which interfered with the assessment is the fact that several patients were receiving anticonvulsive drugs. Finally, many of the patients were 60-70 years old.

The most frequent complication in our series has been the appearance of thorotrastomas. The great majority of the arteriographies were done by the open method under general anæsthesia, yet the occurrence of thorotrastoma in the neck in our series is approximately 14%. It is our impression that the incidence is higher than in percutaneous arteriography with thorotrast but we have too small a number of percutaneous thorotrast arteriographies to allow accurate comparison. One of the reasons for leakage at the site of the injection by the open method may be the fact that the injected vessel has no surrounding supporting structures, these having been removed by dissection.[7] It is also possible that at cut-down arteriography the artery is stretched and flattened by traction on the tape that is passed around the artery below the needle, thus favouring puncture of both anterior and posterior walls of the artery and injection of part of the contrast material outside the vessel. We suggest that arteriography by the open method with thorotrast should be done only after considerable deliberation and preferably by passing a small catheter into the artery. When this procedure is undertaken, it is important to include the site of the needle in the lateral radiograph of the skull so that if extravascular injection or extravasation does take place it will be visualized. We would like to stress that deposition of contrast media of any type around the carotid artery or within its wall may partly or completely occlude its lumen and as a result may be responsible for many of the neurological sequelæ attributed to the so-called toxicity of the contrast medium itself.

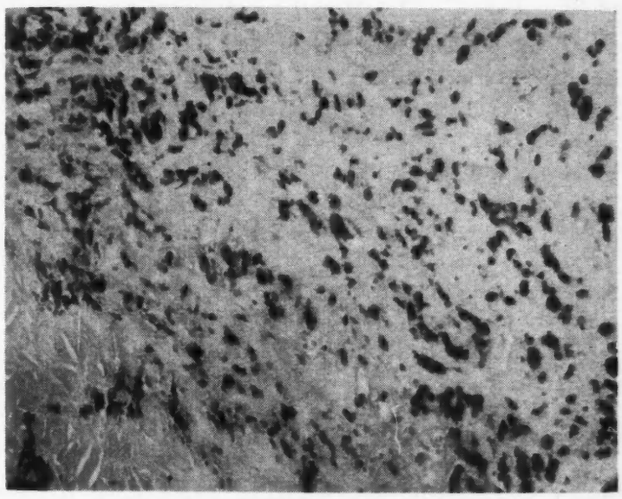


Fig. 3(a).—Low-power view of an old thorotrastoma showing dense fibrous connective tissue. Some granules of thorotrast are seen intracellularly in the macrophages and also loose in the connective tissue.

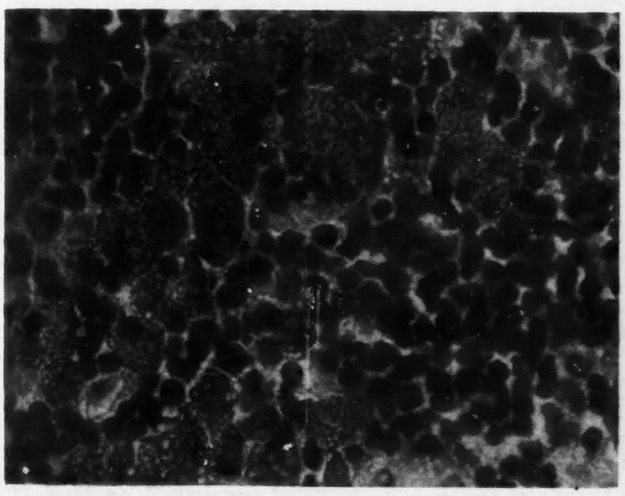


Fig. 3(b).—High-power section from a cervical lymph node of the same case. The small dark cells are lymphocytes. The large cells filled with granular, highly refractile, foreign material are macrophages.

Canad. M. A. J.
June 15, 1958, vol. 78

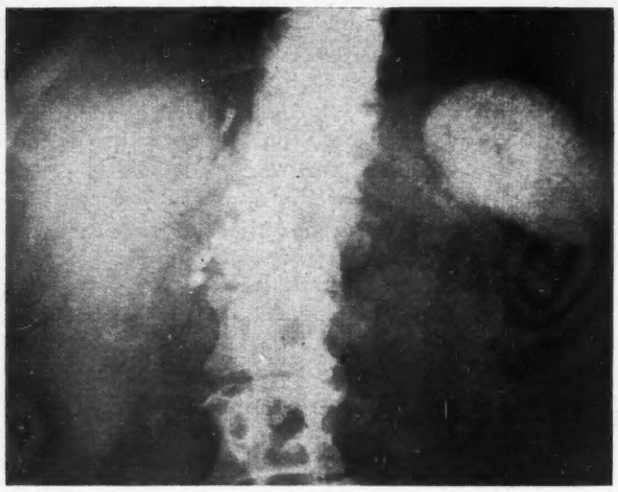


Fig. 4.—Radiograph of the upper abdomen 19 years after intracarotid injection of 20 c.c. of thorotrast. Note the fairly homogeneous, dense liver shadow, the spotty dense spleen shadow, and the dense lymph nodes of the porta hepatis.

Radiographic Findings

The deposits in the neck have been mainly small and asymptomatic, but there were five examples of large deposits causing symptoms. The deposits are densely opaque, partly because of thorium and partly because of calcium in the tissues. An extensive right-sided thorotrastoma is shown in Fig. 2. This particular case was complicated by laryngeal paralysis. One other case presented with a left-sided thorotrastoma responsible for a considerable degree of discomfort in the left side of the neck. This patient was operated upon and as much of the granuloma as possible was excised (Fig. 3). The operation was followed by laryngeal paralysis and did not alleviate pain in the left side of the neck.

The liver presents a more or less homogeneous increase in density and with time it tends to diminish in size and perhaps in density. This has been noted also by Seaman.[20] The lymph nodes in the region of the porta hepatis showed deposits of thorium or calcium in 24 out of the 26 cases radiographed. They may overlie the lumbar spine and thus be overlooked. Films of the abdomen soon after the thorotrast injection never show these nodes. This probably indicates that some drainage of thorotrast towards these lymph nodes takes place from the liver and spleen. Soon after injection of thorotrast the spleen shows a uniform increase in density. Years later the spleen presents very fine, discrete, dense nodules or granules 1-3 mm. in diameter. This probably indicates some re-distribution of thorium or calcium in the spleen. The edge of the spleen is generally sharp. Follow-up studies indicate that diminution in the size of the spleen usually takes place.

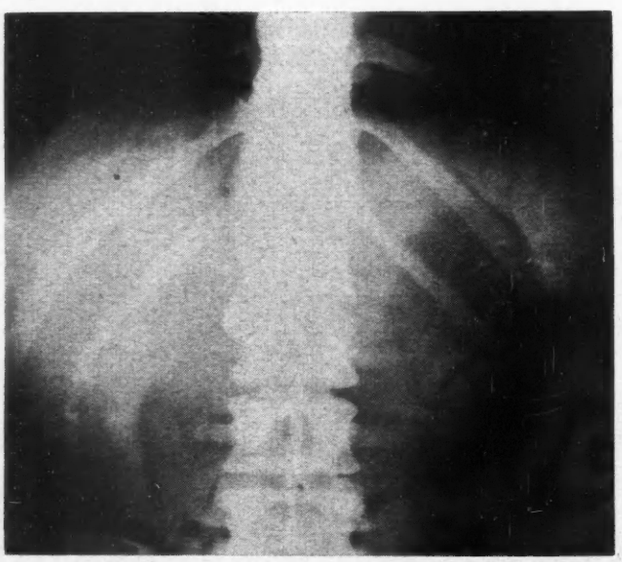


Fig. 5.—Radiograph of the upper abdomen 11 years after intracarotid injection of 30 c.c. of thorotrast. Note the homogeneous quality of the liver shadow, the nodular appearance of the spleen shadow and the radio-opaque lymph nodes in the cœliac region.

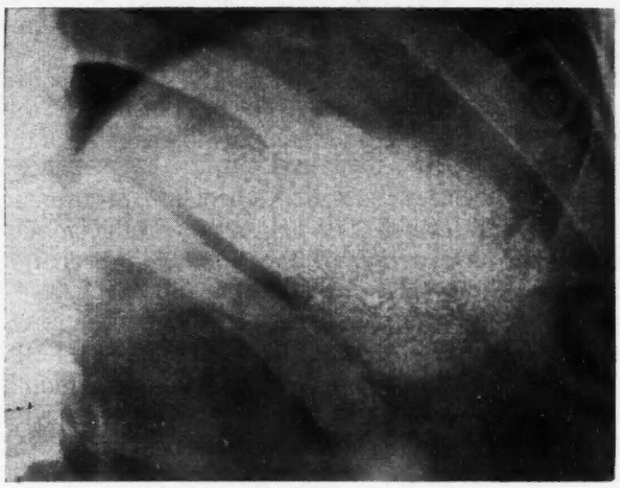


Fig. 6.—Radiograph of the spleen 18 years after intracarotid injection of 20 c.c. of thorotrast.

The appearances described in the liver, spleen and glands of the porta hepatis seem to be characteristic. If such appearances are not noted, one would consider the possibility of a thorotrastoma in the neck and insufficient contrast material having entered the blood stream to opacify the abdominal organs.

We found no characteristic changes in the radiograph of the chest.

We noted no disturbance of the bony architecture in the tibia and fibula, although coarsening of the trabecular pattern and thickening of the middle of the shafts of the long bones was described by Looney in 1950.

CONCLUSIONS

One hundred and thirty-four patients who had had thorotrast carotid arteriography 5 to 22 years previously have been followed up.

The most frequent complication in the series has been thorotrastoma of the neck.

Three of the 134 patients died of malignancy other than brain tumour. These represent as diverse forms of malignancy as found in any sample of the population, and the frequency is no

greater than would be found in a population of similar age and sex followed for an equal period of time.

The minor hæmatological changes noted in two patients are not conclusive.

No definite conclusions should be made from the small number of cases studied with regard to significant increase in malignancy of the liver or spleen or leukæmias. The study of larger series is essential for more adequate evaluation of the entire problem.

Thorotrast is an extremely useful substance for the study of the long-term effect of small quantities of internally deposited radioactive material. In view of its extremely long half-life, long-term follow-ups are essential for the study and evaluation of this substance. As our patients have been followed up for an average of only 12½ years, the present communication should be regarded as a preliminary one. Its value will obviously be considerably enhanced if the patients at present alive are followed up in order to determine the cause of death.

We wish to thank L. G. Stephens-Newsham, Ph.D., and R. M. Cunningham, M.D., of the Royal Victoria Hospital for determining the body radioactivity in some of these patients.

REFERENCES

1. BACKER, O. G.: Peripheral blood changes following internal contamination with radioactive material (Colloidal Thorium Dioxide), reprinted from Progress in radiology, Proceedings of the fourth International Conference on Radiobiology held in Cambridge on August 14-17, 1955, edited by J. S. Mitchell *et al.*, Charles C Thomas, Publisher, Springfield, Ill., 1956.
2. National Academy of Sciences, Washington, D.C.: Biological effects of atomic radiation, National Academy of Sciences—National Research Council, Washington, D.C., 1956.
3. BUDIN, E. AND GERSHON-COHEN, J.: *Am. J. Roentgenol.*, 75: 1188, 1956.
4. CASSEL, C. *et al.*: *A.M.A. Arch. Int. Med.*, 88: 42, 1951.
5. CORBETT, B. D. *et al.*: *Physics Med. & Biol.*, 1: 37, 1956.
6. Editorial: *J. A. M. A.*, 108: 1656, 1937.
7. ELVIDGE, A. R.: Personal communication, 1956.
8. Finsen Institute: Reports, 1949-1953, Finseninstitute, Copenhagen.
9. International Conference on the Peaceful Uses of Atomic Energy: Proceedings Geneva 1955, Vol. II, Biological effects of radiation, United Nations, New York, 1956.
10. JOHANSEN, C. *et al.*: Internal radioactive contamination, Finsen Institute Reports, 1949-1953, Finseninstitute, Copenhagen.
11. LEVY, L. F.: *Brit. J. Surg.*, 43: 638, 1956.
12. LOONEY, W. B.: *Am. J. Roentgenol.*, 72: 838, 1954.
13. *Idem*: *Ann. Int. Med.*, 42: 378, 1955.
14. LOONEY, W. B. *et al.*: *Am. J. Roentgenol.*, 73: 1006, 1955.
15. LOONEY, W. B. AND COLODZIN, M.: Study of late effects following thorotrast administration, paper delivered before the 55th Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September, 1954.
16. LOONEY, W. B. *et al.*: *A.M.A. Arch. Path.*, 60: 173, 1955.
17. MCMILLAN, G. C. (Montreal, Canada): Personal communication, 1956.
18. Great Britain, Medical Research Council: The hazards to man of nuclear and allied radiations, Her Majesty's Stationery Office, London, 1956.
19. ROTBLAT, J. AND WARD, G. B.: *Nature, London*, 172: 769, 1953.
20. SEAMAN, W. B.: Personal communication 1956.
21. THOMAS, S. F., HENRY, G. W. AND KAPLAN, H. S.: *Radiology*, 57: 669, 1951.
22. Council on Pharmacy and Chemistry: *J. A. M. A.*, 99: 2183, 1932.

RÉSUMÉ

L'emploi du thorotrast ou de la diagnothorine pour l'artériographie cérébrale a été introduit par Moniz en 1931. Ces produits opaques aux rayons X contiennent de l'oxyde de thorium, produit radioactif dont la période est de 1.65×10^{10} années. Ce sel forme une suspension insoluble dans l'eau et qui flocule dans le courant sanguin. Le système réticulo-endothélial en capte 90% alors que les autres 10% sont excrétés dans l'urine dans les 48 heures qui suivent l'injection. Le thorium lui-même ne produit que des particules alpha, mais ses produits de désintégration libèrent des rayons beta et gamma. Son maximum de radioactivité n'est atteint qu'une vingtaine d'années après sa déposition dans les tissus. Les auteurs du présent article ont entrepris de faire l'analyse des symptômes et signes cliniques présentés par une série de 134 malades ayant reçu du thorotrast pour angiographie cérébrale par voie intra-carotidienne. Ces malades furent suivis pendant une période de 5 à 22 ans (moyenne 12½ ans). On ne put rejoindre que 26 des 68 survivants. Ceux que l'on examina montrèrent un clocher de radioactivité à l'endroit du foie, de la rate et du cou, et 14% d'entre eux portaient un thorotrastome à l'endroit de l'injection, causé sans doute par l'infiltration des tissus au cours de l'intervention. Par ailleurs l'interprétation des résultats de l'examen clinique présenta une difficulté remarquable car la plupart d'entre eux étaient porteurs de lésions cérébrales graves et plusieurs étaient encore sous traitement anti-comitial; de plus ce groupe comprenait plusieurs sexagénaires. Des 66 malades décédés, 51 périrent des suites de la lésion pour laquelle on avait eu recours à l'artériographie. Dix autres moururent d'une manière accidentelle sans rapport à leur lésion intracranienne ou à la présence de thorium dans leur système. Deux moururent dans les quelques heures qui suivirent l'examen, dont un d'hémorragie que l'on pourrait à la rigueur attribuer à une fibrinopénie qu'on a déjà observé en présence de thorium. On compta trois cas de néoplasie (estomac, plancher de la bouche, et poumons). Cette proportion par rapport au nombre d'individus et à la période d'observation est sensiblement la même que l'on trouve dans la population en général.

Le degré d'invalidité causée par les granulomes dépend beaucoup plus de leur site anatomique et des structures impliquées que de ces tumeurs mêmes. Les néoformations vues chez ceux qui ont reçu du thorium sont d'interprétation compliquée. Les opinions à leur sujet sont partagées, certains anatomo-pathologistes les prétendent bénignes alors que d'autres les croient fatales. Les même remarques s'appliquent aux modifications de la formule sanguine (leucopénie, lymphopénie etc.) Les cas d'anémie aplastique ou de leucémie ne sont pas assez nombreux pour qu'on puisse en tirer des conclusions probantes. L'occlusion des carotides par déposition périartérielle de tissu cicatriciel peut être responsable des reliquats neurologiques que l'on attribue au thorotrast. Il n'est pas impossible qu'une partie de l'action sclérosante des injections provienne d'une irritation causée par le véhicule dans lequel le thorotrast est en suspension. Les auteurs font remarquer qu'en vertu de la période trés prolongée du thorium une observation beaucoup plus longue que celle qu'ils ont été à même de faire jusqu'à présent est nécessaire avant qu'on puisse tirer des conclusions définitives.

NONTUBERCULOUS PNEUMONIA COMPLICATING PULMONARY TUBERCULOSIS

The characteristics of 47 cases of nontuberculous pneumonia occurring in 36 patients with pulmonary tuberculosis are presented by LaBarbera *et al.* (*Ann. Int. Med.*, 48: 635, 1958). The results are compared with previous series presented in the literature, all covering the era before antituberculous chemotherapy and before the newer antimicrobials were available. The absence of mortality from the pneumonia and the low incidence of exacerbation of the tuberculosis by the pneumonia are in contrast with earlier series. Nontuberculous pneumonia occurred in 4.3% of 695 tuberculous patients treated during a 1½-year period while under the personal supervision of the authors. Yet an examination of the records at the hospital revealed a substantiated pneumonia listed among the final discharge diagnosis in only 0.3% of 2074 patients treated in the previous 10-year period. Few of the pneumonias presented the picture of a classic lobar pneumonia, and it is concluded that the incidence of the combined diagnoses rose with awareness. A relationship between the status of the tracheobronchial tree and resolution of the pneumonia is tentatively suggested by bronchoscopic and bronchographic examinations. Emphasis is placed on importance to the patient of making the correct diagnosis and the effect on ventilatory insufficiency of the pneumonia in an already damaged lung.

Canad. M. A. J.
June 15, 1958, vol. 78

TETANUS NEONATORUM*

MAUREEN H. ROBERTS, M.B., Ch.B., D.C.H.,†
Halifax, N.S.

TETANUS in the neonatal period is fortunately now rare in the more civilized areas of the world, so it is with some chagrin that I report six cases all occurring in the space of four years from an area within 30 miles of this city. The cases occurred in a rural Negro community whose way of life is certainly primitive in spite of television sets and numerous electrical appliances. The normal births occur at home under the direction of one of the local "handywomen" whose usual occupation involves contact with animals. These women have had no formal training and use their own methods to treat the umbilical cords. These are said to be daily dressings of soft paraffin dug from the container by finger and applied on gauze. I am informed by the provincial health authorities that 94% of the births in this province take place in hospital. Of the rest, a few are conducted at home by country doctors or Victorian Order nurses. The remainder of the mothers fend for themselves in one way or another. The poverty of the Negro community described above would in itself probably deter the mothers from coming to hospital unless the birth were complicated.

CASE 1.—Baby T, a male child, was admitted on December 8, 1953, aged 15 days—the twelfth child of healthy parents. The history was of inability to open his mouth because of stiffness of the jaws since the ninth day, and a day or two later stiffness of the arms and legs. The midwife changed the dressing on the cord daily but it had not healed well. The baby was unconscious and rigid when examined; he relaxed somewhat at times but stiffened to opisthotonic spasms when there was any external stimulus, especially noise. The umbilicus was moist and dirty, but only *Staphylococcus epidermidis* and diphtheroids were obtained on culture. Treatment consisted of immediate intravenous injection of 10,000 units tetanus antitoxin followed by 10,000 units intramuscularly every six hours for three days. Terramycin, 50 mg. intravenously, and penicillin, 100,000 units intramuscularly, were given every four hours. The child was nursed in a quiet, dark room and was fed intravenously. Oxygen was given as necessary and suction frequently used. Phenobarbital grain ½ intravenously and paraldehyde 10 to 15 c.c. by rectum were used as required to control the spasms and stiffness. He slowly recovered and was discharged five weeks later, healthy.

CASE 2.—Baby C, a male child, was admitted on May 31, 1954, aged six days—the seventh child of healthy parents. This baby was a cousin of Baby T. There was a history of generalized convulsions starting on the day of admission. The baby was in severe continuous opisthotonos with generalized convulsive movements in addition. The umbilicus was infected and culture revealed *Staphylococcus pyogenes* and a heavy growth of *E. coli*. Blood culture was negative. The cerebrospinal fluid was pale yellow and cloudy and showed 17 cells per c.mm., protein 110 mg. %, chlorides and sugar normal, culture sterile. In spite of 20,000 units tetanus antitoxin intravenously immediately and a further 20,000 units intramuscularly every 24 hours, together with 1,000,000 units penicillin every 24 hours, the baby died on the fourth day. While it lived the baby was sedated with phenobarbital and paraldehyde. At autopsy there was hæmorrhage into the air spaces of the lungs but no pneumonia. The umbilical infection was apparently localized and the liver was normal. The cerebral vessels were congested but there was no cerebral hæmorrhage or other abnormality.

CASE 3.—Baby R, a male child, was admitted on July 22, 1954, aged seven days—the eighth child of healthy parents. There was a history of stiffness of the jaw of one day's duration and an infected umbilicus. On examination, the baby had spasm of the arms and legs, opisthotonos and extreme spasm of the jaw. From the infected umbilicus a heavy growth of *Staphylococcus pyogenes* and *E. coli* was obtained. The C.S.F. was slightly blood-stained; it contained 5 white blood cells and many red cells per c.mm., proteins 59 mg. %; chlorides and sugar normal, culture sterile. This baby was treated on lines similar to the foregoing—20,000 units tetanus antitoxin every four hours intravenously and 200,000 units penicillin every four hours also intravenously. Sedation was with intravenous paraldehyde—1.5 ml. of a 5% solution as required, together with phenobarbital grain ¼ intravenously as required. Succinylcholine was given to this baby who, on the fourth day, required a tracheotomy through which his respirations were with difficulty maintained by a mechanical breather. Intracardiac adrenaline started the heart beat on three occasions when he apparently died, but he failed to respond on the sixth day. The autopsy showed a left pneumothorax but all other organs including the central nervous system were grossly normal. Postmortem cultures from the umbilicus were unsuccessful.

CASE 4.—Baby C, the granddaughter of the midwife who delivered Case 3, was admitted on August 11, 1954, aged seven days—the thirteenth child of healthy parents. There was a history of rigidity of one day's duration, particularly marked in the face, and generalized convulsions had been taking place over the same period. The baby was in a state of spastic rigidity with risus sardonicus, immobile jaw and continuous generalized convulsions. She was treated with 20,000 units tetanus antitoxin intravenously immediately and every four hours thereafter. In addition, 200,000 units penicillin was given intravenously every four hours. Umbilical culture gave a growth of *Staphylococcus pyogenes* and *Streptococcus fæcalis*. C.S.F. was slightly yellow with a coagulum, 3 cells per c.mm., protein 90 mg. %, culture sterile. This baby also required a tracheotomy which was done on the day of admission. A Pentothal drip was set up to control the convulsions, but the amount required to achieve this caused cessation of respiration and it was discontinued. The baby died on the third day. Autopsy revealed extreme congestion, recent hæmorrhages and patchy collapse of the lungs.

*From the Department of Pædiatrics, Dalhousie University.
†Associate Physician, The Children's Hospital, Halifax, N.S.

CASE 5.—Baby S, a male child, was admitted on May 9, 1955, aged six days—the third child of healthy parents. There was a history of "stiffness" of one day's duration, and on the day of admission he was "shaking all over". On examination, this premature Negro infant was opisthotonic and had spasms of board-like rigidity at the slightest stimulus. C.S.F. showed a small coagulum, cells increased, protein 122 mg. %, culture sterile. No organisms were cultured from the umbilicus. Treatment consisted of 20,000 units tetanus antitoxin intravenously every six hours and 1,000,000 units penicillin every four hours. The baby was given paraldehyde intravenously as a sedative. He died on the second day. Autopsy showed nothing remarkable.

CASE 6.—Baby D, a female, was admitted to hospital on February 1, 1957—an illegitimate child. The birth was said to have been normal by the midwife, who herself brought the baby to hospital because it had developed a "cold" on the day before admission. On examination, the baby was in generalized tonic spasm with risus sardonicus, flexed and rigid upper extremities, retracted neck and board-like abdomen. The umbilical stump was infected and showed a blood-stained exudate. Her breathing was irregular and ineffective, a tracheotomy being necessary on the fourth day. Tetanus antitoxin 20,000 units intravenously was given initially and 1000 units were injected around the umbilicus; 20,000 units were then given daily intravenously. In this case an attempt was made to control the spasms with succinylcholine, the baby being mechanically ventilated by means of a Jefferson respirator. The baby's colour improved initially but ventilation was clearly inadequate and she later became progressively cyanosed, dying on the fifth day. Autopsy consent was not obtained.

DISCUSSION

Tetanus neonatorum is a disease which should not occur in communities where a high standard of hygiene and nursing care for the newborn is claimed. Where geographical or economic factors increase the proportion of home confinements, we may perhaps expect an increase in the incidence. However, home confinements of themselves need not lead to tetanus, as is shown by the figures from England where a large proportion of births are conducted at home, yet only 22 deaths due to neonatal tetanus were registered in the ten years 1946-1955 out of a population of 47 millions.[1] Case reports in the English language have been few in the last ten years. Jelliffe[2] records 25 cases from the University College Hospital, Ibadan, Nigeria, within six months, 24 of these being from one tribe whose ways were extremely primitive. From a community more like ours were the 26 cases reported by Spivey[3] in New Orleans. He comments on the apparent racial selection of the victims, the proportion of Negro to white being four to one, although the proportion for general admissions at the same time was only two to one.

The Mitchell-Nelson textbook[4] states that in tetanus the cerebrospinal fluid is normal but may be under some increase in pressure. Many textbooks make no mention of C.S.F. changes, suggesting that these are rarely prominent in this disease. Because of this, the C.S.F. changes in four of our cases were of particular interest. In all, a considerable rise in protein was found with little or no increase in cell count, and no evidence of intracranial hæmorrhage in the three cases coming to autopsy. In no case was the diagnosis of tetanus confirmed by culture of *Cl. tetani* from the umbilicus, but the clinical picture was most suggestive and no other cause for generalized convulsions of this severity was found. There was no evidence of septicæmia in any case and the paucity of post-mortem findings was itself suggestive of tetanus.

The treatment given to these cases followed the lines usually advocated and in general must be regarded as quite ineffective. Tetanus antitoxin was given to all cases at the earliest opportunity intravenously and supplementary doses either intravenously or intramuscularly. With the exception of Case 2, all cases received doses within the normally accepted therapeutic range. There is no unanimity among the experts as to the ideal dose or the mode of administration, but there seems to be a growing feeling that a single large dose of antitetanus serum given as early as possible may be as effective as continuous treatment (Spivey[3]). On the other hand Johnstone,[5] in a recent article reviewing the treatment of one hundred adult cases in Nigeria, questions the efficacy of early large doses and in fact doubts the usefulness of serum at any stage in established tetanus. We have had experience of tetanus in an older child who responded satisfactorily to a course of continuous therapy only to relapse one week later and require a second full course of antiserum.

As in many other reported series, it was found difficult to set a dose of sedative which would adequately control the spasms without dangerously depressing respiration. Only two of our infants received muscle-relaxant drugs and we feel we cannot comment usefully on the efficacy of this treatment. More recent reports indicate that chlorpromazine may be useful in producing relaxation in combination with other sedatives, which are then effective in much smaller dosage. Packard, Cartmill and Henry[6] described the use of chlorpromazine in large doses intravenously in the treatment of two older children suffering from tetanus. They comment on the gratifying control of muscular spasms and the absence of respiratory depression. This therapy would surely be worthy of trial in the neonate, in whom the high mortality of the disease would justify the use of this potentially hepatotoxic drug.

The prognosis is depressing. Jelliffe reports no recoveries in his 25 cases. Spivey had a recovery rate of 23% in a series of 26, the recoveries being almost entirely in those cases developing the disease after the seventh day.

Canad. M. A. J.
June 15, 1958, vol. 78

SUMMARY

Six cases of neonatal tetanus are reported. All originated in a rural Negro community over a period of less than four years. Treatment was orthodox. Only one infant survived.

The recent literature on neonatal tetanus is briefly reviewed and recent trends in treatment are discussed.

I wish to thank Professor G. B. Wiswell and Dr. N. B. Coward for allowing me access to the records of cases treated on their services.

REFERENCES

1. Personal communication—Registrar General of the United Kingdom.
2. JELLIFFE, D. B.: *Arch. Dis. Childhood*, **25**: 190, 1950.
3. SPIVEY, O. S., GRULEE, C. G. JR. AND HICKMAN, B. T.: *J. Pediat.*, **42**: 345, 1953.
4. NELSON, W. E., ed.: Mitchell-Nelson textbook of pediatrics, 5th ed., W. B. Saunders Company, Philadelphia, 1950, p. 515.
5. JOHNSTONE, D. D.: *Brit. M. J.*, **1**: 12, 1958.
6. PACKARD, R. S., CARTMILL, T. B. AND HENRY, J. G., *Ibid.*, **1**: 16, 1958.

RÉSUMÉ

Le tétanos des nouveau-nés est une entité nosologique relativement rare dans le monde civilisé, cependant en moins de quatre ans l'auteur a pu en colliger six cas issus des faubourgs nègres de Halifax. Ces nourrisons étaient tous nés à domicile sous les soins de sages-femmes dont les connaissances d'asepsie étaient sans doute des plus rudimentaires. Dans chaque cas l'infection, contractée probablement par contamination animale, pénétra par voie du cordon ombilical. En dépit des méthodes habituelles de traitement appliquées avec toute l'intensité possible, et basées sur l'emploi d'antitoxine, de terramycine, de pénicilline et de phénobarbital, un seul des ces petits malades survécut. La fréquence de ces cas réflète le niveau d'hygiène du milieu où ils se produisent. On observa une élévation de la teneur protidique du liquide céphalo-rachidien sans augmentation du nombre des éléments formés, trait qui ne semble pas avoir été décrit jusqu'à présent. L'auteur reconnaît qu'en aucun cas fut-il possible de confirmer le diagnostic par la culture du bacille de Nicolaïer, mais elle déclare que le tableau clinique ne laissait subsister aucun doute.

HYPERSENSITIVITY TO PENICILLIN*

D. S. MUNROE, M.D.,† *Vancouver, B.C.*

PENICILLIN is the most widely used antibiotic, and in the United States it is estimated that 350 tons are distributed annually. Reactions to penicillin used in the prevention or treatment of a great variety of disease have become the most frequent of all drug reactions. These reactions to penicillin vary widely in severity from a mild skin lesion to sudden death, and it has been estimated that over 1000 deaths[1] have resulted from its use in the United States. Penicillin is said to cause more deaths at present than foreign protein injections. However, the exact frequency of reactions to this antibiotic is unknown because neither the minor nor the severe ones have been reported fully. Meyler[2] states that reactions occur with the following frequency: crystalline penicillin, 1.2%; penicillin in oil and wax, 2.7%; procaine penicillin, 1.4%; penicillin in non-allergic people, 1.5%; penicillin in allergic people, 3.8%.

In a recent report Maganzini[3] quotes the incidence as follows: 2 to 2.5% of children; 5% of non-allergic adults; 15% of allergic subjects. Feinberg and Feinberg[1] estimate that reactions occur in 1-5% of patients treated with the drug.

Most authors seem to agree that reactions are less frequent and less severe in children, that previous penicillin therapy leads to much more frequent and more severe reactions, and that reactions to oral therapy are less frequent than those which follow parenteral administration. It seems to be generally agreed that any type of penicillin can cause any of the reactions caused by any other preparation of the drug, and that procaine is rarely the cause of reactions induced by procaine penicillin preparations. Antihistamines will not prevent a reaction in a highly hypersensitive person. These statistics and opinions should surely support the often expressed opinion that penicillin should be used only where therapeutic necessity exists, and that its indiscriminate use exposes the population at large to the dangers of sensitization.

TYPES OF REACTIONS TO PENICILLIN[2-4]

It is the purpose of this report to mention briefly the various types of reactions to penicillin, with particular attention to some of the serious lesions which may result from its use.

Local reactions at the site of injection are infrequent, but staphylococcal and Gram-negative bacillary infections are occasional complications, especially of prolonged therapy. General reactions are numerous. Fever with or without other manifestation is occasionally caused by penicillin, as is arthralgia.

A wide variety of allergic skin lesions varying in type from generalized pruritus to exfoliative dermatitis and purpura occur. The commonest skin lesion is the urticarial reaction with or without angioneurotic œdema. Scarlatiniform or morbilliform rashes may occur. The time of onset and the severity of the skin lesions are widely variable. Siegal[4] states that it is possible that acute disseminated lupus erythematosus may be induced by penicillin, and that a positive L.E. phenomenon has been seen in patients with penicillin sensitivity reactions. Transient pulmonary infiltrations of the

*Presented at the Pacific Northwest Regional Meeting, American College of Physicians, Seattle, Wash., January 17, 1958.

†From the Department of Medicine, Vancouver General Hospital.

Loeffler type, acute pulmonary œdema and bronchial asthma are the lesions which may occur in the lungs. Eosinophilia is common. Thrombocytopenic purpura, leukopenia and agranulocytosis have been reported.

Anaphylactoid shock is the most severe of all the reactions to penicillin and is not infrequently fatal. A brief review of the histories of two patients recently seen serves to underline this point.

CASE 1.—W.B.G., male, aged 33. On the evening of July 10, 1957, this man took orally one tablet of penicillin containing 400,000 units for an acute sore throat. Within ten minutes he developed severe anterior chest pain which was soon accompanied by difficulty in breathing. A little later he walked to the bathroom in response to an urge for a bowel movement, went unconscious, recovered consciousness in a few minutes, and had a large involuntary bowel movement. The chest pain and dyspnœa continued and he was again unconscious when his doctor arrived. Severe pruritus had meanwhile developed but there was no skin lesion. At that time, peripheral pulse was imperceptible and his blood pressure was 50 mm. Hg systolic. He was transferred immediately to the Vancouver General Hospital.

When first seen by the author, approximately 1½ to 2 hours after he had taken the penicillin, he was complaining of severe chest pain and dyspnœa. His skin was reddened generally and he had a few urticarial lesions in both flanks. His hands and feet were stiff and slightly swollen and he seemed to have some facial swelling. Pruritus was still intense. The blood pressure was 80/60 mm. Hg. The patient was evidently recovering and had already received morphine grain 1/6 (10 mg.). He was given oxygen and diphenhydramine hydrochloride (Benadryl) intramuscularly with progressive improvement. He was well the next morning.

The patient was kept in hospital for several days. Radiographs of the heart and lungs, and serial electrocardiograms were normal. The differential leukocyte count showed 9% eosinophils on the day after admission.

The patient's family history was negative for allergic diseases but his history suggests that he may have had asthma in childhood. At the age of 22 he had a full course of penicillin for the treatment of primary lues.

CASE 2.—V.G., male, aged 47. This patient had rheumatic heart disease with mitral stenosis. On June 12, 1957, commissurotomy was performed by Dr. Ross Robertson. The patient's postoperative course was uneventful. He received streptomycin for a short time during the postoperative period and penicillin throughout his hospital stay which ended on June 28, 1957. On July 26, 1957, he was given benzathine penicillin G, 1,200,000 units intramuscularly, by his physician. He immediately became pale and was dead within one minute. Autopsy showed no cause for his death.

Anaphylactoid shock due to penicillin, as with other causes, presents with alarming suddenness and severity. Sudden faintness, pallor, unconsciousness, and even convulsions can occur. Severe dyspnœa with or without wheezing may be present. Anterior chest pain or retrosternal pain may be the chief complaint. The pulse may be imperceptible and blood pressure severely reduced or unobtainable. A skin lesion may be present and if this is clearly of an allergic type, diagnosis may be facilitated. Death may quickly ensue. If it does not soon follow and therapy is promptly given, complete recovery can be expected.

The diagnosis of anaphylactoid shock due to penicillin is usually quite easy, provided one is aware of the possibility and provided one knows that the patient has taken penicillin. On the other hand, the arrival of a patient in an emergency ward in such a state that no history can be obtained may make the diagnosis virtually impossible in the absence of some overt allergic manifestation such as urticaria. Case 1 exemplifies the fact that anaphylactoid penicillin reaction may simulate acute myocardial infarction; the shock, the retrosternal pain and the dyspnœa had been at first considered as being possibly due to the latter. The diagnosis became clear with the history of ingestion of penicillin, the history of generalized pruritus, and the few urticarial lesions on the abdomen. It is easy to imagine circumstances in which the differential diagnosis would include the causes of coma and convulsions—and the diagnosis must be quickly made for effective therapy to be carried out.

The treatment of anaphylactoid shock consists of the usual measures for a severe allergic reaction —maintenance of an airway, epinephrine, antihistamines parenterally, aminophylline intravenously, and oxygen. Pressor substances and blood transfusion may be required for protracted shock. Adrenal steroids given intravenously are of value.

Hypersensitivity angiitis[2, 5, 6] has been reported in a number of instances in patients who have been receiving penicillin in addition to other antibiotics and drugs. However, no case report of this entity has been encountered in which penicillin alone has been used. On the other hand, there is good reason to believe that penicillin, like many other allergens, can cause this severe vascular lesion.

PREDICTION OF HYPERSENSITIVITY REACTION TO PENICILLIN

Perhaps the most important facts on which to suspect that a patient will react adversely to penicillin are to be obtained from his history. A family or personal history of allergic reactions or diseases is important. This applies particularly to asthma. The incidence of penicillin reactions is higher in allergic than in non-allergic individuals. Particular inquiry should be made about previous penicillin therapy even if no reaction occurred. An overwhelming number of patients who get reactions have had previous therapy. The patient, however, may not know, or may not be able to tell, of previous therapy with penicillin, for several reasons which include the following: previous ther-

Canad M. A. J.
June 15, 1958, vol. 78

apy in childhood, or abnormal mental states, such as during anæsthesia or when only partially recovered from anæsthesia; previous use of such potent sensitizers as penicillin troches, ointments, or contaminated syringes. Boiling does not destroy the antigenic properties of penicillin. The percentage of reactions is still further increased in those who have had previous reactions. Those in whom previous reactions occurred early after therapy are in a particularly hazardous position.

The technique and value of skin tests[3, 4, 7-9] in predicting reactions to penicillin is a subject of considerable debate in the literature. Several techniques involving the scratch and intradermal methods have been used. Tuft *et al.*[8] feel that the best intradermal method is the use of 0.02 ml. of a solution containing 10,000 units per ml. A scratch test may be made first if extreme sensitivity is suspected. A dangerous degree of sensitivity is indicated by an immediate positive reaction, marked by erythema and wheal formation within 20 minutes. Smith[9] applies a drop of procaine penicillin (300,000 units per ml.) to a skin scratch and to the conjunctiva. If no reaction is visible in 20 minutes, the drug may be given. He recommends that skin testing be done at the beginning of each new course of penicillin therapy.

The use of skin testing has, however, several limitations which include the following: (1) After a sensitivity reaction to penicillin, the skin test may remain positive for a very short time only.[7] A negative skin test may thus yield a false sense of security. (2) The mere skin testing of a hypersensitive individual can be highly dangerous.

To summarize the present state of our ability to predict penicillin reactions, one can express the opinion that no matter how careful the physician may be he cannot, by any method at present available, predict all reactions to penicillin either in those who have had previous penicillin therapy or in those who have no knowledge of previous therapy. The history of a previous reaction should take precedence over a negative skin test.

TECHNIQUE OF ADMINISTRATION OF PENICILLIN

In view of our present inability to predict fully those patients in whom penicillin therapy will result in an adverse reaction, the technique of administration of the drug is of some importance. Particular care should be taken in those patients to whom penicillin therapy was given several weeks or more previously. Some prefer to give the first dose orally because of the reduced chance of anaphylactoid shock, but deaths have been reported after use of the oral route, even in early childhood.[10] Others[4] recommend that the first dose be given in the arm so that a tourniquet may be applied proximal to the site of the injection should an immediate reaction occur. Intravenous injection should be meticulously avoided. Epinephrine should be immediately available. Medical personnel should be well versed in the technique of administration and in the immediate therapy to be applied in the event of adverse reaction. Anaphylactoid shock is a medical emergency of the utmost urgency and one in which immediate therapy may make the difference between life and death.

PENICILLINASE

The use of this enzyme in therapy in recent months has led to predictions that it will be a very valuable adjunct in the control of allergic reactions to penicillin. This enzyme is produced by many bacteria including staphylococci and *E. coli*. It was discovered in 1940 and heretofore it has been used by bacteriologists to hydrolyze and inactivate penicillin. The resultant product is non-allergenic and non-antibiotic. In May 1956, Becker[11] demonstrated in guinea-pigs and in humans that parenteral injection of this purified enzyme resulted in extremely rapid disappearance of detectable penicillin from the blood. A single injection of the enzyme kept the blood free of the antibiotic for several days, even though injections of penicillin were continued twice daily. No toxic effect was noted.

Minno and Davis[12] in September 1957 reported a series of 42 cases of allergic reaction to penicillin treated with the drug. This group did not include any case of anaphylactoid shock. The dose used was one million units intramuscularly as a single dose and occasionally this dose was repeated in several days. No toxic reactions were encountered. The usual result was prompt relief of itching and relief of the reaction in a few hours. It is understood that in the *Antibiotics Symposium* (October 3, 1957) which is in the press, further favourable reports will be seen on the use of penicillinase. It is hoped that prompt use of this enzyme, perhaps intravenously, will be effective against anaphylactoid shock due to penicillin in all except that minority of patients who die instantly. Intravenous injection of the enzyme, however, has itself resulted in a reaction.[12]

The use of penicillinase has also been suggested as a diagnostic test in certain allergic states or skin reactions. A recent allergic reaction which persists in spite of penicillinase is probably not due to penicillin. It has also been used in a prophylactic manner in patients known to be allergic to penicillin and who require poliomyelitis vaccine or other substances containing penicillin.

SUMMARY AND CONCLUSIONS

Reactions to penicillin are common. The time of onset varies from immediate to several weeks after exposure, and the effect from minor to fatal.

The factors which predispose to hypersensitivity reactions have been mentioned. Chief of these are an

allergic background and previous penicillin therapy, especially with a previous reaction to the antibiotic.

It is impossible at present to detect by any or all methods all individuals who are allergic to penicillin.

Anaphylactoid shock due to penicillin with or without death has resulted from administration of the drug by the oral as well as the parenteral route.

Penicillinase promises to be a safe and an extremely effective agent in the treatment of allergic reactions to penicillin.

The writer is indebted to Dr. A. W. Wallace of Vancouver for permission to quote Case 1, and to Dr. J. G. M. McMurchy of Nelson for permission to quote Case 2.

REFERENCES

1. FEINBERG, S. M. AND FEINBERG, A. R.: *J. A. M. A.*, 160: 778, 1956.
2. MEYLER, L.: Side effects of drugs, Elsevier Press, Inc., Houston, 1952.
3. MAGANZINI, H. C.: *New England J. Med.*, 256: 52, 1957.
4. SIEGAL, S.: *New York J. Med.*, 56: 2859, 1956.
5. ZEEK, P. M.: *New England J. Med.*, 248: 764, 1953.
6. TALBOTT, J. H. AND FERRANDIS, R. M.: Collagen diseases, Grune & Stratton, Inc., New York, 1956.
7. BERGER, A. J. AND EISEN, B.: *J. A. M. A.*, 159: 191, 1955.
8. TUFT, L., GREGORY, D. C. AND GREGORY, J.: *Am. J. M. Sc.*, 230: 370, 1955.
9. SMITH, V. M.: *New England J. Med.*, 257: 447, 1957.
10. MASON, L. H.: *Canad. M. A. J.*, 76: 958, 1957.
11. BECKER, R. M.: *New England J. Med.*, 254: 952, 1956.
12. MINNO, A. M. AND DAVIS, G. M.: *J. A. M. A.*, 165: 222, 1957.

RÉSUMÉ

Les incidents du traitement à la pénicilline sont devenus fréquents. On peut les observer de quelques instants à plusieurs semaines après l'administration du médicament, et leurs effets varient d'une éruption passagère jusqu'aux complications les plus graves. Les facteurs prédisposants à l'hypersensibilité comprennent des antécédents allergiques, tels que l'asthme, ainsi qu'une exposition antérieure au médicament, surtout s'il y a eu réaction fâcheuse. Il n'existe à l'heure actuelle aucune méthode qui puisse désigner avec certitude les sujets allergiques à cet antibiote. L'administration *per os* n'est pas sans danger puisqu'on a déjà rapporté des cas de choc anaphylactique avec mortalité même, tout comme avec les autres modes d'administration. La pénicillinase semble un moyen prometteur de combattre ces réactions.

EXCHANGE TRANSFUSION IN THE NEWBORN USING HEPARINIZED BLOOD*

G. H. VALENTINE, M.R.C.P., D.C.H., F.R.C.P.[C.], *St. Thomas, Ont.*

EXCHANGE or replacement transfusion of the newborn is now a widely used and established technique for the treatment of severe states of jaundice in the newborn when the jaundice is of the hæmolytic type or is due to the indirect-reacting, or unconjugated, bilirubin. Exchange transfusion is, of course, most commonly used in the treatment of hæmolytic disease of the newborn due to incompatibility of the rhesus factor, but with the appreciation that mortal danger to the infant lies in the degree of jaundice as much as in its cause, exchange transfusion is being more and more employed. In hæmolytic disease of the newborn due to incompatibility within the ABO system, the jaundice may become of such degree that the baby is in peril from kernicterus, and exchange transfusion is quite commonly required. Even in severe examples of so-called physiological jaundice the danger of kernicterus may arise; and this danger threatens even more the premature baby who seems especially liable to brain damage by bilirubin.

For the baby with rhesus factor disease, the exchange transfusion accomplishes simultaneously four desirable actions. It replaces blood with a high bilirubin level by blood of a normal level of bilirubin. Thus the danger of kernicterus may be obviated. It removes blood containing harmful antibodies and replaces it with blood without such antibodies. It removes blood which is susceptible to destruction (since it is of a group upon which the antibody can act) and substitutes for it blood which, not possessing that group, is insusceptible to destruction. It supplies, in exchange for blood which may be of low hæmoglobin content, blood of normal hæmoglobin concentration. Few procedures in medicine perform so simply and elegantly four simultaneous therapeutic functions.

For the baby with ABO hæmolytic disease, the first three of these functions are of importance. Anæmia of any severity is unusual.

For the baby with "physiological" jaundice in danger of kernicterus, the most important function of exchange transfusion alone is operative: the lowering of the bilirubin level.

In the past, it has been a common practice for such procedures to be carried out in the larger centres, but they are now quite frequently used in small hospitals. It might therefore be helpful if the experience in technique gained in smaller hospitals were to be passed on. Moreover, in the last two years all exchange transfusions were carried out with heparinized blood and it may be of value to record the results of this method which is not in general use.

The methods here described have been evolved over a ten-year period, during which time nearly 100 exchange transfusions have been done personally. During the years 1948 to 1950, the cases were seen in a large centre handling most of the cases from a population of about 400,000 in an English urban community. From 1950 to 1953, the cases were from an English rural district and were treated in one of three small hospitals of between 200 and 300 beds, serving together a population of

*From the St. Thomas-Elgin General Hospital, St. Thomas, Ontario.

Canad. M. A. J.
June 15, 1958, vol. 78

about 150,000. From 1954 to the present time, the cases are drawn from Elgin County in Ontario, a mixed urban and rural district where all deliveries are in hospital. The St. Thomas-Elgin General Hospital has 350 beds and deals with about 1000 deliveries annually. The detailed records of the English cases are not readily available, nor are the numbers exact, but in about 70 cases up to 1953 there were, during the exchange transfusion itself, three deaths which could be ascribed to the procedure. In these early cases, citrated blood was used, and in some cases blood which had been stored for several days was given. The deaths may well have been due to hyperkalæmia in the donor blood, citrate intoxication or poor technique.

The St. Thomas series, which starts in August 1954, forms the matter of this paper. There have been no deaths either as the result of the procedure or as the result of hæmolytic disease. It is true that one baby in the series died of sudden unexplained respiratory paralysis at six months and was found at autopsy to have cerebral atrophy, but this baby never showed more than a very slight degree of jaundice and required no treatment. It is doubtful if the death and hæmolytic disease are more than coincidental.

The procedures described are those at present in use, although there have been some changes over the three years covered by this paper.

MATERIAL

Table I shows the material managed by methods described in this paper. All but two of the cases were seen and treated personally. Before the middle of 1955, we were not recognizing ABO hæmolytic disease for what it was. Thus in this survey, the ratio of ABO disease to rhesus disease is less than we have since shown it to be.

TABLE I.

Rhesus incompatibility	
Babies not requiring treatment	4
Babies requiring exchange transfusion	12
Number of exchange transfusions	17
ABO incompatibility	
Babies not requiring treatment	14
Babies requiring exchange transfusion	6
Number of exchange transfusions	8
Unexplained jaundice, "physiological"	
Babies requiring exchange transfusion	1
Number of exchange transfusions	1
Total number of deliveries during period under review	3438
Number of babies with hæmolytic disease, ABO and rhesus	36
Number of exchange transfusions	26
Number of exchange transfusions with heparinized blood	21

INVESTIGATION

Unfortunately, but few of our cases were predicted by antenatal antibody studies, and it was clinical suspicion of disease that prompted investigation in the majority.

Usually it was the early onset of jaundice that initiated investigation, and any baby with jaundice within the first 24 hours after birth was fully investigated, for it is our experience that this is always abnormal and almost certainly indicates hæmolytic disease. Occasionally, before the onset of jaundice, pallor, a stained liquor or a yellow-stained cord raised suspicion of hæmolytic disease.

The first step is the determination of the ABO and rhesus blood groups of the mother and baby, together with the direct antiglobulin test of Coombs on the blood of the infant. In the first instance, the rhesus factor D is tested. In the early days, it was judged adequate to do a slide test, but two false results led to routine tube testing of the rhesus groups. If the mother is rhesus-negative (cde/cde), the Coombs test positive and the baby rhesus-positive (D), it is a fair assumption that the baby has hæmolytic disease due to D incompatibility and that antibody anti-D is responsible.

If the Coombs test is positive and there is no incompatibility of D, it is likely that the hæmolytic disease is due to one of the more unusual antibodies. The blood of both mother and baby is then tested by tube agglutination for factors C and E individually. We have found one case where anti-E was the sole antibody. We have not knowingly encountered hæmolytic disease due to Kell or Duffy.

We have found (to be published elsewhere) that hæmolytic disease in the newborn is three times more commonly due to ABO incompatibility than to rhesus incompatibility. ABO disease is usually a quite benign condition, which can well escape notice, but it is not always so. It is to be suspected in a baby who becomes jaundiced within 24 hours of birth, in whom the Coombs test by the usual technique is negative or very weakly positive, in whom no rhesus incompatibility can be found and where the baby is either A or B (or AB) and the mother group O.

In the baby where rhesus incompatibility exists and the Coombs test is positive, we have assumed this incompatibility to be the cause of the disease, and further immediate investigation is directed to establishing the severity of the condition. The rapidity of onset of the jaundice and the degree of pallor, together with the general condition of the infant, are some guide. But one can be deceived. Cord blood samples are now routinely saved from all deliveries and are kept stored for this further investigation, should they be required. On these cord blood specimens, the bilirubin and hæmoglobin levels are estimated as a guide to the management of the case.

Where ABO hæmolytic disease seems likely, certain confirmatory tests are carried out. These babies have a microspherocytosis and an increased reticulocyte count. The presence of the former in particular would tend to confirm a suspicion of ABO disease. Until recently, we used the antibody

enhancement test of Witebsky, as described by Davidsohn,[1] to furnish further proof of ABO hæmolytic disease. In this test, the whole blood of a baby with ABO disease should agglutinate on a slide within 90 seconds when mixed with complement-inactivated normal AB serum. We found this test difficult to interpret and prone to give false positive reactions. The two-stage test for free antibody described by Zuelzer and Cohen[2] is now used. This test appears to be very reliable and quite simple. The antibody in the baby's serum is made to act upon cells of the same group as the baby, but with fully developed antigenic potency; namely, cells from an adult. We use as test cells the blood of the father. If his baby has the disease, he can only have blood of the right group to use for the test. After the serum of the baby has been allowed to act upon the washed cells of the father, there will be, in a positive test, either a visible fine agglutination or, on further testing, a positive Coombs test. We now accept this as evidence of ABO hæmolytic disease.

Finally, blood samples from mother, father and baby are sent to a laboratory specializing in immunohæmatology for confirmation of our findings, for antibody studies and for genotyping—the latter so that a more informed prognosis can be given for future pregnancies.

SELECTION FOR TREATMENT

At one time, it was our policy to carry out exchange transfusions on all babies with a positive Coombs test, and this policy worked well, but no doubt unnecessary exchanges were done. Since the publication of the paper of Walker and Neligan,[3] exchange transfusion is done under the following circumstances: (1) When the baby is premature, under 5½ lb. (2) When a previous baby has been severely affected. (3) When the cord blood hæmoglobin is below 15 g. %. (4) When the cord blood hæmoglobin is above 15 g. % but the cord blood bilirubin above 2.8 mg. %. (5) If at any time the serum bilirubin rises to 20 mg. % or above. In a baby under 5½ lb. one might set a limit of 17 mg. % as the upper limit of safety, and in a very small baby one should perhaps regard 15 mg. % as dangerous. It is important to have some clear criteria in mind. These have been entirely satisfactory.

If a case is rejected for immediate exchange transfusion, the baby is watched closely. If it becomes at all deeply jaundiced, repeated capillary blood bilirubin estimations are carried out, regardless of the hour of day or night. They may be required as often as every three hours if the bilirubin is high and rising. To manage these cases correctly and safely, the laboratory must be able to give this service.

If an exchange transfusion has been done, the same close watch is kept. If the bilirubin rises to 20 mg. % or above (less in a small baby), a further exchange is performed.

In ABO disease, an immediate exchange is not done, but the degree of jaundice and the bilirubin level are watched with the same vigilance. A level of 20 mg. % (less in a small baby) is accepted as an indication for immediate exchange transfusion.

It has not been our practice routinely to give vitamin K. Severely sick babies are nursed in an incubator, as are all who have had an exchange transfusion. However, as soon as the condition is satisfactory, the baby is treated as though normal. There is no reason why the babies should not be breast fed.

EXCHANGE TRANSFUSION

Since November 1955, we have used heparin as an anticoagulant rather than citrate, in the belief that it is preferable. The heparin can be added in a very small volume, and thus the hæmoglobin concentration of the donor blood is not reduced by dilution. It has also seemed possible that the large amounts of citrate given when citrate is the anticoagulant may be responsible for the deterioration in condition which in the past was not infrequently found during the course of the procedure.*

Since heparinized blood has been used, no problems have been encountered and the babies remain in much better condition throughout the replacement.

In the period up to 1954, blood was drawn from a blood bank, and while efforts were made to ensure that it was as fresh as possible, it occasionally happened that blood which had been stored for several days was used. Some of the severe reactions and even the three deaths may have been due to this. Now all blood used for exchange transfusion is given within an hour of bleeding the donor, who is selected from a panel of volunteers or professional donors living in the town. Until very recently, specially prepared silicone-coated bottles were used, 1500 units of heparin in 1.5 c.c. being added just before the collection of the blood. Now, silicone-treated bottles already containing 1500 units of heparin are available commercially (Abbott Laboratories). It is doubtful if there is any special advantage in the silicone coating for exchange transfusion.

We have felt that we should not be satisfied with an exchange of less than 80 c.c. per lb. body weight, and for an average baby we have taken 600 c.c. into the 1500 units of heparin. With a large baby, we have used two donors and two bottles.

For babies with rhesus disease, one should use rhesus negative (cde/cde) blood of the same ABO group as the baby. We have frequently used group O blood with the addition of A and B substance without mishap in a baby of group A or B.

Babies with ABO hæmolytic disease are treated with group O blood to which 10 c.c. of A and B substance (Sharpe & Dohme) has been added, for

*See addendum.

each 600 c.c. This is added to reduce the concentration of natural antibodies anti-A and anti-B present in group O blood. The rhesus group should, of course, be the same as that of the baby, or else the blood should be rhesus-negative.

We do not remove any plasma from the donor blood, nor do we use specially selected donors with low antibody titres.

The compatibility of the donor blood with that of the baby is checked thus. Two suspensions of the donor cells are made—one in saline, the other in bovine albumen. An equal quantity of the baby's serum is added to each and both are centrifuged for 10 minutes. Agglutination is checked macroscopically and confirmed microscopically. The tube with donor cells suspended in saline together with the baby's serum is then incubated at 37 degrees for 30 minutes, the cells are washed three times, Coombs reagent is added, centrifuged for one minute and checked macroscopically and microscopically for agglutination.

Exchange transfusions are now carried out in the operating room with the operating room staff and full aseptic ritual. The apparatus is prepared, sterilized by autoclaving and stored in a central supply room where it is immediately available. It is put up in two unit packs. One consists of a complete set of fine dissecting instruments, together with sutures and ligatures. All that might be required for a saphenous cut-down is in this pack. The other contains the special syringe, together with its adapters and delivery tubes of clear plastic, two medium-sized basins, one 2-c.c. syringe and medium needles and one Resiflex Infant Feeding Tube of clear plastic, 15 inches long, size 8 French. Both units are held in duplicate in case of accidents or sudden further demand.

The special syringe, a 20-c.c. Direct Flow Transfusion Syringe (Allen & Hanburys, cat. no. 16486), is the vital instrument for the procedure. Several devices have been tried but nothing has been found so simple, rapid and trouble-free in use as this three-way syringe. It has been used exclusively for the past seven years. It has not been seen in similar use elsewhere.

The procedure can be conducted by the operator and one good nurse, but two nurses are preferable. One nurse has as her prime duty the keeping of the record of how much blood has been exchanged. A resuscitator is ready for immediate use.

The apparatus is assembled as shown in Fig. 1, the discard tube being to the left and the inlet for the donor blood to the right. The centre nozzle is for the umbilical catheter. Into one of the basins is poured sterile saline and enough heparin is added to make a solution of 100 units per c.c. With this the syringe and the tubes are thoroughly flushed.

The baby is brought to the operating room in an incubator and fixed on a frame as for circumcision. The abdomen and cord are cleaned with Merthiolate and towels placed so that the face remains

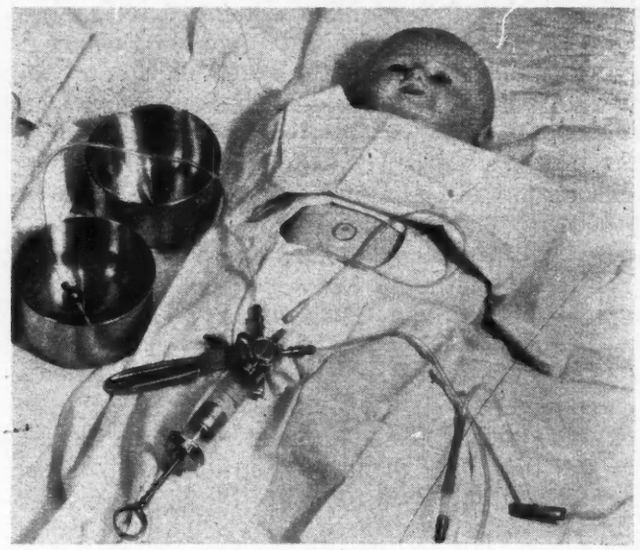


Fig. 1.—Apparatus assembled for exchange transfusion showing three-way syringe, connecting tubes and plastic umbilical catheter.

visible to the operator. A towel with a central hole covers all except the umbilicus.

The apparatus is now arranged on the towels with the discard basin to the left and the heparin-saline basin alongside for washing the apparatus further if necessary. The right tube is connected to the donor blood and the control clip opened. The barrel and piston of the syringe swing in an arc and can be selectively opposed to each of the three nozzles. Blood is drawn from the right nozzle, the syringe is then opposed to the centre nozzle and a little blood discharged to fill the nozzle, and lastly it is swung to the left discard outlet and air bubbles are expelled.

The cord is then cut off flush with the skin, for to do so greatly facilitates entry of the vein, which can be easily seen as a patulous vessel compared with the tightly constricted umbilical arteries. The vessel is steadied with forceps and the feeding tube passed down the vein until blood flows freely. The tube is then attached to the centre nozzle. As a rule, no anchoring of the tube is necessary, but a single suture may be put through the skin edge and tied around the plastic tube to fix it. The umbilical vein remains patent for several days and we have used it without trouble six days postnatally. Only once has the saphenous vein been used in the last five years, in a baby 12 days old.

Using the plastic tube described, we have found no difficulty in entering the baby's circulation, nor, with this large tube, has any difficulty been encountered in withdrawing blood. We have not routinely measured the umbilical vein pressure, but exchanges have been run below equality. For the first four or five changes, one may remove 15 c.c. and replace 10 c.c. so that the baby is in deficit of 20-25 c.c. It is our impression that, with heparin as an anticoagulant, it is not really necessary to run the exchange at a deficit. Nevertheless, we have observed this precaution. One may use 10 or 20 c.c. aliquots. The former is less likely to

upset the circulatory dynamics. Using this syringe and tube, one can proceed at a rapid rate and it is possible to complete a full exchange in 30 minutes. However, such haste is neither necessary nor desirable.

In theory at least, the more slowly the exchange is conducted the more effective it will be in clearing bilirubin. If the baby shows signs of distress, the procedure should be halted for a few minutes. Yawning, sighing, smacking of the lips and excess salivation have in the past appeared to be danger signals which must be seriously regarded. Provided the baby is crying, one can be assured that all is well. If serious signs of shock develop, the exchange must be stopped, 30 or 40 c.c. withdrawn immediately and oxygen given. The exchange may have to be abandoned and perhaps resumed some hours later. A baby showing signs of trouble can die in a matter of moments. We have not, however, seen any signs of this shock syndrome since we started to use heparinized blood straight from the donor. We have not given calcium gluconate with heparinized blood.

When the required volume of blood has been exchanged, the tube is withdrawn and the skin margins approximated with fine sutures over the umbilical cord root so that it may be kept clean and fresh should another exchange be required. We have not used protamine sulphate to neutralize the heparin and have met with no bleeding problems apart from a slight ooze of a few drops for an hour or two on occasion. Antibiotics have not been given as a routine.

Commonly, the last withdrawal of blood has been kept for bilirubin estimation, and values of from 3 to 7 mg. % have been found. Following the exchange, close watch is kept and frequent bilirubin estimations are made, as indicated above.

FOLLOW-UP

After the acute stage is past and the jaundice cleared, hæmoglobin estimations are performed every week until one is sure that the hæmoglobin is not dropping. A simple transfusion is given if the hæmoglobin falls below 9 g. %.

When full details of the maternal antibody and paternal genotype are known, the outlook for future pregnancies is discussed with the parents. Nowadays, it is felt that one need never give a really gloomy outlook. Finally, the mother is given a letter with full details of her blood groups and antibodies so that easy reference can be made in the event of future pregnancy or the necessity for receipt of a blood transfusion.

SUMMARY

The management of hæmolytic disease of the newborn in a county hospital of moderate size is described in detail. The use of a three-way syringe in simplifying technique and the advantages of heparinized blood are emphasized.

My thanks are due to the many doctors who have sent these cases to me. It is a pleasure to acknowledge my gratitude to the many who have helped in this work, especially to the laboratory technicians who have been so long-suffering.

The Ortho Research Foundation, Raritan, New Jersey, most kindly performed the antibody studies and genotype tests and I am most grateful to the director, Dr. Philip Levine.

Abbott Laboratories most generously supplied the silicone bottles for clinical investigation.

ADDENDUM

Since the completion of this paper, the work of Firt and Hejhal[4] on the toxic effects of citrated blood in large transfusions has been published. They show that citrate may cause heart failure during large rapid transfusions. This experimental work adds considerable weight to the clinical impression reported here that the severe and occasionally fatal shock syndrome observed when citrated blood is used for exchange transfusion does not occur with heparinized blood.

BIBLIOGRAPHY

1. DAVIDSOHN, I.: *Obst. & Gynec.*, 8: 318, 1956.
2. ZUELZER, W. W. AND COHEN, F.: *Pediat. Clin. North America*, 405, May, 1957.
3. WALKER, W. AND NELIGAN, G. A.: *Brit. M. J.*, 1: 681, 1955.
4. FIRT, P. AND HEJHAL, L.: *Lancet*, 2: 1132, 1957.

RÉSUMÉ

L'exsanguino-transfusion est devenue un moyen reconnu de traiter les dyscrasies hémolytiques du nouveau-né comme celles qui résultent de l'incompatibilité Rh ou ABO. L'auteur fait part de l'expérience acquise au cours d'une série de 21 transfusions de sang hépariné. Ne disposant pas des facilités de laboratoire nécessaires au dépistage de ces réactions dans la période prénatale, l'auteur surveille les signes cliniques à l'accouchement et au cours des premières heures de vie. Les cas suspects sont soumis à une épreuve directe de Coombs et à la recherche du facteur Rhésus D. Ces deux épreuves suffisent dans la grande majorité des cas; dans les autres, les facteurs C et E sont aussi recherchés. Les indications de ces transfusions sont formulées dans le texte. L'héparine obvie aux inconvénients que présente le citrate par son accumulation dans la circulation. L'auteur préconise l'emploi d'une seringue avec robinet à triple effet. La dose habituelle de sang est de 80 cc. par livre (175 cc./kg.). Une description détaillée de la technique employée à l'hôpital général St. Thomas-Elgin termine cet article.

MUSCLE INVOLVEMENT IN BOECK'S SARCOID

Of 42 patients with proved sarcoidosis, reported by Wallace *et al.* (*Ann. Int. Med.*, 48: 497, 1958), 23 showed sarcoid lesions on *random biopsy* from skeletal muscle. There was no consistent correlation between objective changes in muscle and the presence of lesions. The wider the dissemination of the sarcoidosis, the more likely the muscle biopsy was to show sarcoid lesions. The sarcoid granuloma in muscle was similar to that in other tissues. One patient was found with a granulomatous arteritis in muscle due to sarcoid. Because of the sparsity of lesions, routine sectioning at multiple levels proved to be of great importance in discovering sarcoid lesions in muscle.

Canad. M. A. J.
June 15, 1958, vol. 78

SEASONAL ALLERGIES IN SOUTHWESTERN ONTARIO*

JOHN H. TOOGOOD, M.D., F.R.C.P.[C.],†
London, Ont.

EACH OF THE FOUR seasons of the year brings certain allergic problems with it. Seasonal periodicity is evident in many diseases: measles, rheumatic fever, poliomyelitis, peptic ulcer, erythema nodosum. But it is nowhere more conspicuous than in allergic diseases. This is because many of the most potently allergenic materials causing human disease are prevalent only at certain seasons of the year, or because certain environmental conditions, necessary to their allergenic activity, exist for only a few months out of the twelve.

For brevity's sake, I think we might eliminate from consideration such seasonal skin allergies as urticaria and plant dermatitis. I wish to confine my remarks to allergic disease of the upper and/or lower respiratory tract. In this particular clinical entity, which affects to more or less degree approximately 10% of the population, the seasonal periodicity is of real, practical, clinical interest because it may give a strong lead as to the actual agent causing the trouble. Also, one's original clinical suspicion that a primary allergic process underlies a troublesome chest problem must often depend upon one's ability to recognize a characteristic clinical allergy pattern as determined by seasonal variations. Typically, the clinical syndrome is that of rhinitis, i.e. nasal obstruction, itching, sneezing, coryza; or bronchitis, i.e. cough, perhaps with tracheal or bronchial irritation; or asthma (paroxysmal wheezing dyspnœa). These symptoms may occur separately or together, in different combinations or sequences, but basically they all represent various non-specific symptoms of the same condition: chronic allergic disease of the respiratory tract, just as pain, swelling, and loss of function represent different symptoms of a fractured limb; or diarrhœa, tenesmus, nausea and vomiting are non-specific symptoms of disordered function of the gastro-intestinal tract at different levels.

Consider the seasons in rotation, starting with the spring of the year and working round the calendar. In southwestern Ontario rhinitis or asthma in April or early May may be and often is caused by tree pollens. Before the leaves appear on the trees they bud and release pollen. In some species this pollen is of very low allergenicity and its physical characteristics permit it to spread only a small distance from the tree—for example, pine or cedar—and such a tree is of no clinical significance to allergists. However, many other species, such as maple, or oak or elm, release large amounts of pollen that is wind-blown and spreads over large areas.

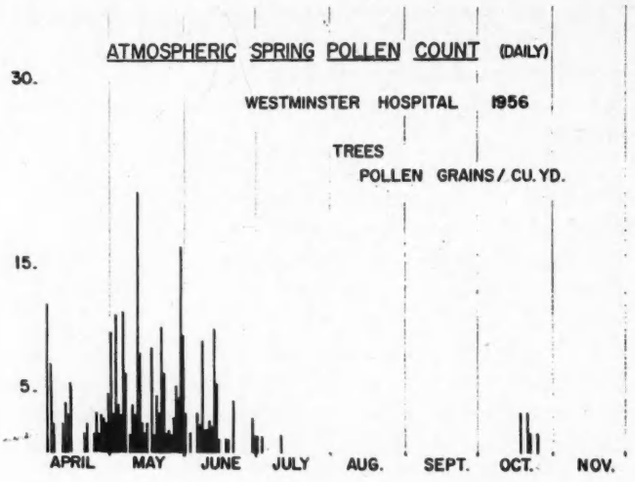


Fig. 1

Fig. 1 shows a graph of tree pollination in the London area in terms of pollen grains per cubic yard for 1956. Differing weather conditions from one year to the next exert a great effect on the time of appearance and the sequence of these peaks of pollination for the different tree species. In general, we can say that each species tends to shed its pollen in large quantities over a short period of a relatively few days or at most a few weeks; and that the difference in tree species from one locale to the next has a marked effect on the frequency of individual allergic cases in the population, as well as on their severity.

About the 24th of May, June grass begins to pollinate in this area and from then until July one species after another blooms and sheds its pollen to be blown for miles over the Western Counties (see Fig. 2). The peak of the season occurs with the pollination of Timothy in early July. Grass pollens disappear between mid and late July—leaving a period of about two weeks' relief for the sufferer from pollen allergy.

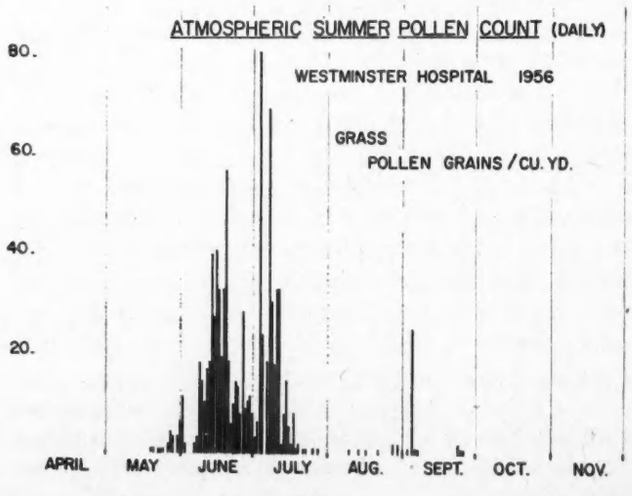


Fig. 2

*Presented to the Huron County Medical Society, October 2, 1957.

†Instructor in Medicine, University of Western Ontario Medical School, and Consultant in Allergy to Westminster and Victoria Hospitals, London, Ontario.

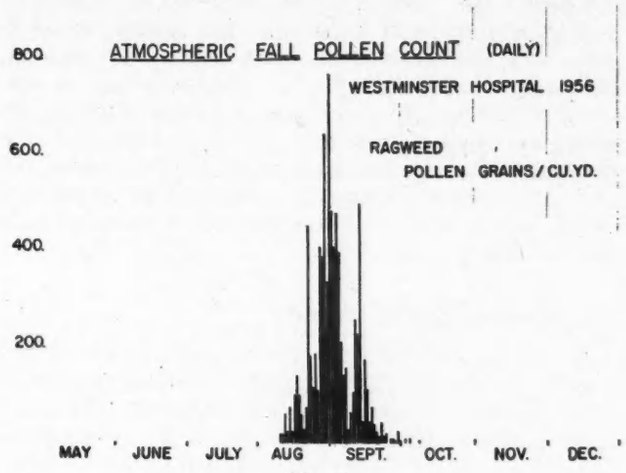


Fig. 3

Then ragweed pollination begins sometime between the 6th and 15th of August, reaching a huge peak around Labour Day and disappearing after the first heavy frost kills the plants in late September or early October (Fig. 3). A variety of other fall weeds contribute actively allergenic pollens at this time, but in the vast majority of clinical cases ragweed is the major offender.

Besides the pollens, airborne mould spores cause a lot of trouble in this region. Exactly how much is hard to say. This is now the subject of active research under a public health grant to the Department of Medicine, University of Western Ontario. Fig. 4 illustrates some mould spore counts in recent years in this region. It is useful clinically to keep in mind the difference in appearance of this graph, with its multiple variable peaks all through the spring, summer and fall, as compared with the pollen graphs with their rather close delimitation to a definite and consistent period during the calendar year. Rhinitis or asthma that varies a lot from one year to the next in time of occurrence and peak of severity may reflect this greater variation inherent in mould sporulation as compared with pollination.

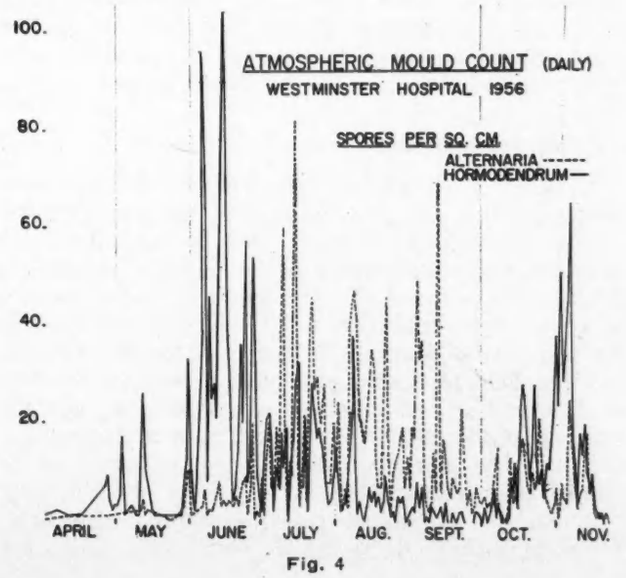


Fig. 4

Individual cases of asthma or rhinitis, of any grade of severity from mild to very severe, may be due to any one of these seasonal summertime allergens. In general, ragweed causes the most trouble, grasses the next, moulds the next, and trees the least, reflecting to some extent their quantitative relationships as illustrated by Fig. 5. It is very common to find people allergic to more than one of these agents and not at all uncommon to have patients allergic to all of them, as well as to numerous other perennial inhalants, foods, etc.

About the time the ragweed pollen leaves the air, i.e. when the cold weather comes, we in this part of the country put up the storm windows, close the doors and revert to our wintertime pattern of indoor living. But most important of all, the heat comes on—and all the accumulated dust of five months' idleness is emptied out of the hot air pipes into the house. The housedust asthma season begins, with symptoms recurring throughout the rest of the fall and early winter months—and very often persisting right through until spring. Although dust is the commonest of the environmental inhalants causing asthma during the winter months, other inhalants such as feathers, kapok, and dog and cat hair, become important at this time. Farmers incur an annual period of increased dust exposure at threshing time, and exacerbations of allergic complaints at that time very often have nothing to do with the seasonally pollinating plants but are related to the current dusty work in progress.

Besides extrinsic inhalant allergens in the winter months, respiratory tract infections are more current. These may be followed by a complicating sinusitis which may be easily evident clinically, or may remain totally occult unless searched for. Severe asthmatic exacerbations in the winter months may be associated with such a lesion. Many sufferers from chronic asthmatic bronchitis of the infective type have a conspicuous tendency for annually recurrent exacerbations in early November and/or early March when peaks of communicable respiratory tract infections sweep through the community.

We have now completed the circuit round the calendar from one spring to the next. Many cases may present symptoms only at one season of the year, but just as many may have trouble at several widely separate seasons of the year, or even all year round, i.e. perennially. This is often due to a broad spectrum of allergies, one allergen after another being encountered in sequence as the calendar year advances. There is also a definite tendency for persons with, let us say, straightforward fall asthma due to ragweed, if left untreated, to progressively develop heightened sensitivity to other inhalants, and even to non-extrinsic types of allergens. As years go by, their asthma tends to persist longer and longer into the winter months and also to appear in June and July with the

Canad. M. A. J.
June 15, 1958, vol. 78

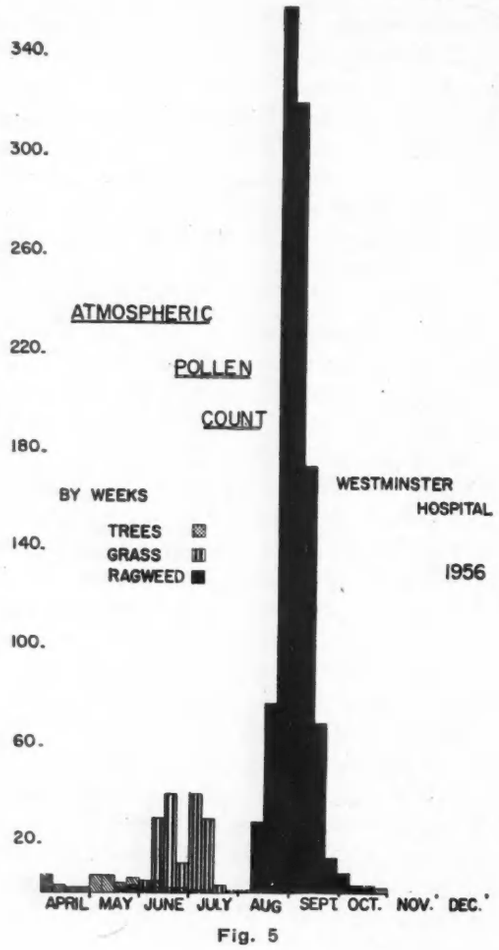


Fig. 5

grass pollens, or even in spring with the tree pollens.

A few case histories help to place these didactic observations in the context of their clinical usefulness. These are chosen to represent common clinical entities and/or general principles, and are arranged in a sequence to permit illustration of various features of their treatment. It will be evident upon review of these cases that allergic disease of the respiratory tract can take various forms: periodic asthma, frequently recurring "colds" and/or pneumonia, bronchitis, chronic headaches—depending on how the admixture of primary allergic symptoms and their secondary complications may alter the pattern in the individual case.

A Summer Headache

CASE 1.—A 29-year-old R.C.A.F. officer complained of severe frontal and paranasal pain coming on acutely during descent from high altitudes. Similar short episodes had occurred under similar circumstances each year for the previous three years, but only during the months of June to July, and August to September. There was no history of frank hay fever or other typical allergic symptoms. On examination the appearance of the nose was that of marked allergy. Allergy skin tests confirmed the clinical impression of sensitivity to grasses and ragweed and he was placed on antihistamine therapy, with an adequate degree of immediate control of these headaches.

Under the special circumstances of R.C.A.F. service an otherwise subclinical hay fever presented with this rather unusual manifestation of seasonal pollinosis: headache. Under the ordinary conditions of civilian life, oral antihistamines alone or an ephedrine analogue would probably constitute the treatment of choice for such cases, but because of the high risk associated with such complaints in operational flying, specific pollen desensitization is mandatory in this instance.

Summer and Fall Asthma

CASE 2—A 27-year-old Italian immigrant developed asthma for the first time in August and September of 1956, his second summer in North America. All symptoms spontaneously cleared after the frost, and recurred in the summer of 1957—but earlier this time: coincident with grass pollination in June. He was seen by various physicians, diagnosed "bronchitis and emphysema", and placed on oral cortisone which controlled his symptoms fairly well for about one month. When disabling asthma recurred as the pollen season advanced, he was referred for allergy study. Skin tests confirmed the clinical story of grass and ragweed allergy, and he was subsequently controlled without the need for steroids.

The immigrant influx in recent years is reflected in the frequency with which this train of circumstances develops after adults with the allergic diathesis become exposed for the first time in their lives to the massive amounts of a highly potent airborne allergen which are found in our ragweed-infested areas. The progressive acquisition in succeeding years of clinical sensitivity to more and more seasonal allergens is quite often seen. In this respect it seems more reminiscent of the common course of events in our native-born children with allergic respiratory tract disease than what we see in native-born allergic adults. Steroids are often of limited value, as in this case, but even if 100% efficient for a time, they should never be prescribed as a substitute for adequate allergy assessment of the case. The indications for initiating allergy investigation and a program of allergy management should not be the failure of steroids to adequately control the symptoms. The better practice would appear to be exactly the opposite, i.e. steroid therapy should not be initiated until adequate cognizance of the allergic aspects of the disease has been taken, which may then avert the need to use them or at least will permit them to be used to their greatest strategic advantage in the immediate and long-range treatment of the individual patient.

Winter Bronchitis

CASE 3.—A 10-year-old boy was said to have been well until the age of 4 years. For the following six winters he suffered a great deal of invalidism and school absenteeism because of winter-long "continuous colds", characterized by unproductive chronic cough, recurrent fever, and only temporary response to multiple antibiotic courses. He was well in the summer months. Skin tests showed a strong positive reaction to house dust and a variety of other seasonal and perennial inhalants. He was placed on dust desensitization and has now gone through two winters entirely free of his former trouble.

A clinical pattern of recurrent febrile bronchitis, recurring consistently in the winter months (only) for

a period of six years, was abruptly halted and has remained so for the succeeding two winters after dust desensitization and dust minimizing measures were initiated in this boy's home. This is an unusual form for allergic disease of the respiratory tract to take. Generally after such a period of time, frank wheezing dyspnœa of either paroxysmal or exertional type, or both, will have manifested itself.

Winter Asthma

CASE 4.—A 35-year-old man had a history of recurrent asthma at sporadic intervals since childhood. For the previous five years a 7- to 14-day-long exacerbation of asthma had annually followed "a cold" in November or December. At the time of referral he was completely disabled by the most recent of these exacerbations which had responded only slightly and very temporarily to therapy with penicillin, a variety of bronchodilators, and prednisone. Sinus radiographs showed unimpressive changes only. An otolaryngologist's opinion was, however, that active frontal and antral sinusitis was present, and Proetz displacements initiated a grossly purulent drainage bilaterally from the nose. This cultured *Streptococcus viridans* in heavy growth and pure culture, sensitive to all antibiotics tested, including penicillin. There was prompt clearing of the asthma after appropriate local treatment to the sinuses to maintain adequate drainage, along with systemic Achromycin.

Occasionally active sinus infection is important in causing persistent severe asthma, and radiographs may be fallible in demonstrating this sinus disease. As in other surgical infections, drainage is equally as important as specific antibiotic therapy, the two measures together performing a job that neither by itself can do as well.

Now, to summarize briefly one's approach to the treatment of these seasonal allergies:

Very minor grades of seasonal allergic disease can be handled by symptomatic medications, such as antihistamines alone.

Steroid hormones should never be used until an etiological diagnosis is made, and a definite plan about the advisability and feasibility of desensitization is formed.

Seasonal allergies of any more than minor grades of severity should be actively treated with desensitization.

A proper plan of desensitization depends upon informed and skilful skin testing.

One cannot skin-test intelligently unless one has taken the patient's history in detail and at first hand.

One cannot intelligently take the patient's history unless one is familiar with the seasonal variations of the different allergens of regional importance. Some of the more important seasonally varying factors in this region have been discussed.

The pollen and mould counts were done in the Allergy Clinic of the Westminster (D.V.A.) Hospital, London, Ontario. We thank the Department of Veterans Affairs for permission to publish these data; Mr. A. Gregor, who made the actual counts; and Mr. D. Pulham, for illustrating the data.

RÉSUMÉ

Les allergies respiratoires du sud-ouest de l'Ontario affectent environ 10% de la population de cette région sous forme de rhinite, de bronchite, d'asthme, etc. En avril et mai les érables, les chênes et les ormes libèrent de fortes quantités de pollens sur des territoires fort étendus, mais cette libération ne dure que quelques jours ou quelques semaines au plus. Vers le 24 mai le pâturin des prés (le foin de vache) commence à se faire sentir suivi de plusieurs autres espèces, jusqu'en juillet. On note une pointe au début de ce mois causée par la fléole des prés (le mil). Après quelques semaines de répit la saison de l'ambroisie trifide (herbe à poux) bat son plein, de la Fête du travail jusqu'aux premières gelées. Les spores de moisissure contribuent à aggraver la situation.

Avec l'hiver commence la période de chauffage des maisons; la poussière accumulée pendant les cinq mois de temps chaud se remet à circuler entraînant avec elle les plumes, le kapok, les poils de chien et de chat et autres menus débris. Les infections respiratoires de cette saison favorisent le terrain au point de vue allergique. On sait d'ailleurs qu'une allergie laissée à elle-même tend à s'étendre et le sujet hypersensible qu'il était à un seul allergène peut le devenir à plusieurs autres.

Les atteintes légères répondent souvent aux simples anti-histaminiques. On ne doit pas recourir aux hormones stéroïdes avant qu'un diagnostic étiologique n'ait été posé et qu'on n'ait étudié les possibilités de la désensibilisation. Cette dernière forme de thérapie basée sur l'anamnèse et la cuti-réaction s'applique à la plupart des allergies saisonnières de quelque importance.

RELAXIN—A CLINICAL REVIEW*

RICHARD X. SANDS, M.D., F.A.C.O.G., M.R.C.O.G.,† *New York, N.Y.*

AMONGST THOSE versed in the physiology of reproduction, it is a matter of common knowledge that the pelvis of several species of mammals is modified during pregnancy to facilitate the birth of the young. This modification is under hormonal control and the hormone is known as relaxin.‡

Relaxin has now reached the same controversial stage in which we found œstrin and progesterone in the early 1930's. Because of this and because a great deal of interest has recently developed in the clinical applications of relaxin, it is important to review the present clinical research picture of this hormone, which together with œstrin and progesterone constitutes the hormonal triumvirate of pregnancy. It is obtained from pregnant sows' ovaries—a rich source—and assayed in terms of guinea-pig units. It is presented in 1 c.c. ampoules

*Based on an address presented at the Annual Meeting of the Canadian Society for the Study of Fertility, London, Ontario, November, 1957.
†The Women's Hospital, New York City.
‡Relaxin is most widely known and most easily available as the commercial product Releasin of Warner-Chilcott.

Canad. M. A. J.
June 15, 1958, vol. 78

containing 20 mg. in saline, equivalent to 3000 guinea-pig units (G.P.U.), or in the form of a repository gel also containing 20 mg./c.c.

Hisaw[1] first described the effect of relaxin upon the pelvic joints in 1926 and later demonstrated the fact that tissue must be œstrogen-primed before it would respond to relaxin. Today, we know that it is a non-steroid hormone, protein or polypeptide in nature, water-soluble, and highly stable.

Its safety has been amply demonstrated by the administration of very high doses. When given by injection, it is rapidly absorbed. One hour after intravenous administration, 50% will have disappeared from the circulation. Varying degrees of absorption have been reported when relaxin is given orally, particularly as a linguet, and more recently therapeutic effects have been maintained with rectal suppositories.

This hormone has been demonstrated in the blood of pregnant women, in concentrations which increase gradually to the 38th to 42nd week, and it disappears rapidly within 24 hours after parturition.[2]

EXPERIMENTAL RESULTS IN ANIMALS

In 1953 Graham and Dracy,[3] studying the problems involved in the transfer of bovine ova, concluded that ease of cervical dilatation was an important factor. They found that although the cervix of the cow could be dilated mechanically during œstrus, it could not be dilated post-œstrus unless the animal had been treated with relaxin after initial œstrogen-priming.

Soon after the above, Zarrow[4] reported similar observations in castrated sows. He found that initial œstrogen-priming followed by relaxin resulted in marked dilatation of the cervical canal. Of equal importance were the results of the histochemical studies of the cervices of the relaxin-treated animals which showed increased permeability, depolymerization of the ground substance, and an increased water content. Zarrow[5] also found that the administration of relaxin increased the water content of the rat uterus from a normal of 80% to 85.3% within six hours and, in addition, that a combination of œstrin and relaxin gave an added increase.

Further to the above, it has also been reported by Steinetz[6] that after a single injection of a repository form of relaxin there is a twofold increase in the glycogen content of the uterine muscle. There is also an increase in total nitrogen and water content.

More recently, Dracy[7] found that after œstrogenization with high doses of diethylstilbœstrol, the bovine cervix relaxed to about six inches in diameter as the result of one injection of relaxin. He also found that another œstrogen-primed animal, when injected with blood from a calving cow, developed cervical dilatation sufficiently great to allow the passage of a calf.

RESULTS IN OBSTETRIC INDICATIONS

Clinically, relaxin has been shown to have a modifying effect upon the uterus and cervix during pregnancy and parturition.[8]

Induction of Labour

Undoubtedly stimulated by the reports of the softening effects of relaxin upon the cervix, investigators have turned their attention to the possible use of this action for the induction of labour in women with a so-called "unfavourable" cervix.

The method which has been found most effective is the administration of 120 mg. of relaxin dissolved in 500 c.c. of 5% glucose in water given by intravenous drip at the rate of 4 c.c./minute. Four hours later, intravenous Pitocin is started. Stone, who devised this method, reported that he had successfully induced labour in 80% of cases having an unfavourable cervix. This was in contrast to 30% in a control group which received Pitocin alone. In a later report on a larger series, there were 71.5% successfully induced compared with 22.8% in the controls.[9] Histochemical analysis of cervical biopsies, removed from relaxin-treated cases, is in progress in an attempt to discover a possible mechanism of action.

This use of relaxin is being further evaluated at one of the Boston maternity hospitals where similarly encouraging preliminary results are being obtained.

Retained Dead Fetus

Until fairly recently, a policy of laissez-faire was looked upon as proper therapy for cases of retained dead fetus. However, since we have learned a great deal more about afibrinogenæmia as a dangerous complication of retention, a premium has been placed upon rapid emptying of the uterus.

Maclure[10] reported a series of 15 cases of retained dead fetus, with fetal ages varying from 4½-6 months and retention *in utero* for intervals of 1-8 weeks. As a precaution, quantitative fibrinogen levels were obtained. All these cases were initially primed with a total of "320 mg. of Releasin in 6 divided intramuscular injections over a period of 12 hours". Intravenous Pitocin was started 18-24 hours later. In 9 cases labour set in within one hour. In the entire series, the uterus was successfully emptied in 13 cases whereas two cases were failures. The labours were short, two patients delivering en bloc. Cervical softening was reported as a consistent finding.

Duration of Term Labour

In a preliminary report, based on a series of over 100 cases of spontaneous primigravid labour, a group working in Miami[11] have found that relaxin reduced the time between 4 cm. and full

dilatation to an interval of 2-3 hours. They also found that the time between 4 cm. dilatation and fetal delivery was shortened to 4-4½ hours. In addition they noted marked perineal relaxation, so much so that two patients who had precipitate labours suffered no perineal laceration.

Another investigator[12] has reported that relaxin was responsible for a remarkable shortening of the duration of labour. This observer used rupture of the membranes and administration of Pitocin as ancillary forms of treatment.

In contrast, at a well-known New York women's hospital[13] relaxin was administered to term primigravidæ alone, as soon as labour was diagnosed. It was found that there was a tendency for the contractions to become desultory and less forceful and to be localized in the region of the lower uterine segment rather than the fundus. In spite of this, the responsiveness of the uterus to Pitocin was not lost and no harm was done.

These clinical observations tend to coincide with those of Kasden[14] who used external tocodynamometry and reported that in 6 out of the 12 cases there was inhibition of uterine contractions after relaxin. It is interesting to note that he found this inhibitory effect most pronounced upon fundal contractions.

McGaughey[15] attempted to demonstrate that relaxin inhibited spontaneous contractility in human uterine muscle strips *in vitro*. He used both gravid and non-gravid tissue but was unsuccessful.

It is interesting to compare the above observations with those of Kelly and Posse.[16] They administered relaxin to a series of women who went into labour spontaneously at term, and studied them with the Karlson internal tocometer. They found that there was no alteration in the uterine contractions of early labour in 24 out of 25 cases.

Further clinical observations, as well as study with the Reynolds tocodynamometer, are in progress in an attempt to clarify the effect of relaxin upon the uterine contractions of early labour.

Premature Labour

Abramson and Reid[17] first drew attention to the effectiveness of relaxin in the treatment of premature labour, setting in between 29 and 31 weeks of pregnancy. They found that this hormone enabled them to prolong pregnancy, in all their cases, through the 36th to 40th weeks.

On the other hand, Eichner[18] reported complete cessation of progressive labour, starting prematurely between 25 and 35 weeks of pregnancy, in only a few of his cases. However, by the use of prolonged high dosage, both intramuscularly and intravenously, he further established the safety of relaxin. In addition to mentioning the salutary effects of the hormone in secondary dysmenorrhœa, he also observed that in his series relaxin brought about a marked degree of cervical softening, an observation shared by Hodgkinson.[18]

Folsome[19] studied a series of 58 patients treated with relaxin, of whom 40 were in premature labour which had set in between 29 and 32 weeks of pregnancy. In this group, fetal wastage was reduced by 61% and the pregnancies were prolonged for intervals varying from a few days (2 cases) to 10 weeks. A further important observation made by Folsome was that the women receiving relaxin experienced less pain during labour and that there was a "fourfold greater incidence of painless precipitate delivery".

More recently, McCarthy,[20] recognizing the diverse etiology of premature labour, studied a series of 15 rigidly selected cases and 15 controls, selected with equal care but the latter receiving no relaxin. It was observed that in all instances relaxin therapy resulted in decreased frequency and regularity of contractions lasting for varying intervals. In those patients who responded completely there was only an occasional mild uterine contraction at the end of 3-4 hours, which could be controlled with periodic relaxin therapy. McCarthy felt that the action of relaxin was cumulative in this group. It is noteworthy that, in the opinion of this investigator, relaxin appeared to be ineffective once the membranes had ruptured.

The positive effects of relaxin upon the generative tract in both animal and human studies appear to be complementary. However, at the moment, the problems of optimum dosage and correct routine of administration still require solution.

RESULTS IN MEDICAL INDICATIONS

Although relaxin is a hormone of pregnancy, often being referred to as the third hormone of pregnancy, it has been found effective in a number of extrareproductive conditions. Chief amongst these is scleroderma.

Scleroderma

In order to study the effect of relaxin upon cholesterol synthesis in pure connective tissue, Boucek[21] devised the sponge-biopsy technique. In essence, the technique consists of the subcutaneous implantation of small pieces of Ivalon sponge which, after varying intervals, become infiltrated with a growth of pure connective tissue and when removed lend themselves to histo-biochemical analysis. During this work it was observed that the animals treated with relaxin developed a very loose skin, and this observation led Casten[22] to begin the study of the effect of this hormone upon scleroderma, for which no effective treatment existed.

For over three years this group observed 23 cases of scleroderma treated with relaxin which was administered either in saline or repository form. The series contained men and women, and the variations in severity of the disease were fairly representative.

Canad. M. A. J.
June 15, 1958, vol. 78

The mode of treatment was to give concomitantly, for a period of two weeks, daily doses of œstrin (Premarin 1.25 mg.) and relaxin in saline (20 mg.). After this, therapy was continued with relaxin repository alone, 20 mg. daily or on alternate days. It was found necessary to continue treatment for 3-5 weeks before improvement could be expected.

In this study,[23] Raynaud's phenomenon, trophic ulceration, and skin tightness were the symptoms which responded most consistently. In addition, skin tightness was observed to respond first at the site of injection. It was found that when therapy was discontinued a relapse might follow after an interval of 3-10 days.

The above work has stimulated a great deal of additional interest, which has resulted in the collection of more data with increased degrees of improvement for the sclerodermic.

The results of an extensive study by Evans[24] at the Lahey Clinic, having already been announced at a staff meeting, are now being prepared for publication. On the basis of Hisaw's original observation that relaxin acted most effectively upon œstrogen primed tissue, this investigator continued the administration of œstrin throughout therapy. The treatment in some cases consisted of a combination of relaxin administration and sympathectomy.

The patients in the series had widespread involvement, especially severe in the hands and face. In addition to the more common symptoms, such as ulceration and Raynaud's phenomenon, many also had pulmonary and gastric manifestations of the disease.

Significantly, dysphagia improved, in some instances so much so that bougie dilatation became unnecessary; paroxysmal dyspnœa and cough disappeared; exertional dyspnœa improved in cases of pulmonary involvement; in a case of laryngeal involvement hoarseness became lessened. In other cases restricted joint movements also improved markedly.

Large-scale study is also in progress, in New York City, by another group who have been treating scleroderma with relaxin for 18 months and whose preliminary results are similar to those above. They have been sufficiently encouraged to prepare their work for publication. In addition, there are innumerable cases of scleroderma in the hands of individual practitioners which have responded beyond expectations to relaxin therapy.

Improvement obtained with relaxin is over and above that possible with the corticosteroids, and more encouraging than that obtained with sympathectomy alone. Unfortunately, the corticoids appear to block the action of relaxin. However, to date, relaxin appears to have a more favourable effect on the disease than any other form of therapy.[25]

EXPERIMENTAL WORK IN PROGRESS

Highly encouraging results are being obtained with relaxin in the treatment of a number of diseases associated with fibrosis. The usual routine consists of initial œstrogen priming followed by relaxin in varying doses. Amongst these conditions are hepato-biliary fibrosis,[26] post-radiation fibrosis lymphœdema, corneal opacity, keloidosis, and fibrous tissue contractures around joints in muscular dystrophy.

In addition, similarly encouraging results have been reported in the treatment of dysmenorrhœa and peripheral vascular diseases. These have been reported in personal communications.

Cholesterol Synthesis

In view of the widespread attention which is at present concentrated upon cholesterol and its association with atherosclerosis, Boucek's[27] work in this aspect of relaxin activity merits particular attention. Very early in his studies with connective tissue biopsies, he had observed that cholesterol concentration in the connective tissue of relaxin-treated animals was lower than in controls. Later, he and his group established the fact that it was the rate of cholesterol synthesis which was reduced. More recently, he attempted to produce the same results by thyroid ablation, by feeding thyroid to hypothyroid animals, and by the administration of tetraiodothyroacetic acid, progesterone, and testosterone. He found that "relaxin was the only hormone studied which caused a reduction in the rate of cholesterol synthesis in the connective tissue of both sexes". This was established by the use of C^{14} labelled acetate. As a casual observation, a patient suffering from hypercholesterolæmia and treated with relaxin had his blood cholesterol lowered from 420 mg. % to 240 mg. %. When relaxin was discontinued it again rose gradually.

Dysmenorrhœa

Academically, dysmenorrhœa is a nebulous condition. However, the patient suffering from pain associated with menstruation must be helped, and since there is no really effective treatment the results obtained with relaxin are of interest.

Studying the non-pregnant organ in 50 women, using the Karlson internal tocometer, Posse and Kelly[28] found that relaxin altered the pattern of uterine contractility. They reported that in dysmenorrhœa fundal contractions of large amplitude and fair duration were exactly coincident with the severe cramp-like pains which the patient felt. Immediately after intravenous administration of relaxin "there was a marked reduction in amplitude, frequency, and duration of contractions". In slightly more than half of the patients who responded, all uterine activity completely ceased. All the patients had definite relief of pain and this relief was coin-

cident with the diminished contractions. It was the opinion of these authors that relaxin strongly inhibited motility in the vast majority of the patients studied, as well as in their cases of dysmenorrhœa.

Furthermore, another investigator experienced in the use of relaxin recently reported his results in dysmenorrhœa. He had obtained markedly encouraging improvement in a series of approximately 200 patients. More recently, another worker,[29] well aware of the psychosomatic aspects of this condition, found that 18 out of 20 girls, aged 16, obtained relief. He felt that "it is more than a coincidence", basing his opinion on the strength of 25 years' experience in treating this particular state.

Other work is in progress and it will be interesting to see what the eventual outcome will be.

More recently relaxin became available in a number of different forms, so that administration need not be exclusively parenteral.

TOXICITY

Eichner used very large doses of relaxin in his studies—as much as 2600 mg. over a period of 24 hours. He used both intramuscular and intravenous routes of administration and in no instance did he observe any indication of toxicity, antigenicity, or sensitivity. On the other hand, two other observers reported "chills", one during the intravenous administration of the hormone in a large quantity of dextrose solution and the other after the administration of 8 c.c., 10 c.c., and 12 c.c. of the hormone solution, undiluted. We have seen one case of extensive urticaria and details of another have been brought to our attention—in both instances it was later established that the patient was sensitive to pork. It should be remembered that the commercially available relaxin is obtained from pregnant sow's ovaries.

In view of the animal origin and protein-like nature of the hormone, the possibility of anaphylaxis must be kept in mind and one case of this has come to our attention. Where this possibility arises, steps should be taken to detect sensitivity and, if present, to desensitize the patient.

However, generally speaking, toxicity is not an important feature of relaxin therapy.

DISCUSSION

Although relaxin is elaborated by the ovaries during pregnancy, and has been shown to affect certain aspects of reproduction, it also seems to act in conditions which are entirely unrelated to pregnancy.

This is probably due to the fact that the action of the hormone is exerted upon one tissue in common, upon connective tissue. Relaxin reverses the aging processes in connective tissue, and from this fundamental physiological activity all the actions of relaxin stem. This is the connecting link, the common bond which links a number of apparently unrelated conditions that have responded to therapy.

Boucek has demonstrated this reversal of the aging process by means of his connective tissue sponge biopsies, which he has grown in both a variety of experimental animals and in humans of different racial types. The aging processes which have been demonstrated in laboratory connective tissue are the same as those formed in blood vessels, chiefly in the intima or in the elastic fibres of the lamina interna, and which account for the diminution in calibre of these vessels.

With aging, the components of connective tissue are altered. The ground substance becomes dense, the collagen fibres are coarse and tightly compressed, the mast cells are few in number, and the tissue has a dry and inelastic appearance under the microscope. In connective tissue biopsies, relaxin has been shown able to reverse this process so that the collagen fibres are finer and more widely separated, the ground substance becomes depolymerized, and there is an increase in fluid inhibition as well as in the number of mast cells. In addition, after relaxin, the metachromatic granules around the mast cell nucleus are altered in their distribution, and this alteration is believed in some way to be connected with the inhibition of cholesterol synthesis by the relaxin-treated connective tissue.

Too many responsible investigators have reported that relaxin is effective in arresting premature labour for this to be a chance observation. However, it is more than likely that this effectiveness is found in a variety of premature labour arising from excessive irritability of the uterus probably caused by a hormone imbalance, possibly of œstrin and progesterone. It is very unlikely that relaxin would have any effect in cases of premature labour arising from fetal death or placental lesions, and in abruptio placentæ or accidental hæmorrhage its use would actually be contraindicated.

Many obstetricians feel that arresting labour during pregnancy and possibly facilitating and accelerating it at term—two of the observed actions of relaxin—are incompatible. However, it is quite possible that the ancillary hormone balance—the concentration of œstrogens and progesterone—may be responsible for this. The high concentration of progesterone during pregnancy may have a synergistic effect upon relaxin and thus be responsible for the inhibitory effect upon uterine contractions. On the other hand, the high concentration of œstrogens at term may be responsible for the almost exclusive effect of relaxin upon the connective tissue of the cervix and in this way facilitating it. The same action which produces the oft-reported cervical softening may also be exerted upon the supporting connective tissue of the body of the uterus, and perhaps in this way alter the contractions of early labour.

However, in spite of the reported alteration of the uterine contractions of early labour, in primigravidæ particularly, the relaxin-treated patient seems to have less pain, is more co-operative, requires less sedation and bears her labour with greater equanimity, so that relaxin could justifiably be described as a uterine anodyne.

Folsome reported that his relaxin-treated patients had less pain during labour and a greater incidence of painless precipitate delivery, an observation also made by the Miami group who, in addition, reported marked perineal relaxation.

The combination of cervical softening and perineal relaxation brought about by relaxin, together with its anodyne effect, should logically result in shortening of labour. This will probably be possible, more consistently, when we have devised a proper technique for the correct use of this hormone, starting early in labour.

The softening effect of relaxin upon fibrosed tissue is as yet to be investigated in the treatment of sterility due to stenosed cervices or to old pelvic inflammatory disease. When pregnancy finally results in this type of case, the incidence of "cervical dystocia" is high and relaxin is indicated in order to facilitate the problems associated with this state.

The effect of relaxin upon cervical problems associated with breech delivery is another indication which should be investigated. There is no doubt that there are also many others.

Few would disagree regarding the biologic importance of a movable pelvic ring during parturition in contrast to the relative rigidity of this ring in the non-pregnant state, hence the softening at the symphysis pubis and at the sacro-iliac joints. However, this basic action of relaxin upon all connective tissue has still to be fully utilized, and its proper place in the hormonal triumvirate of pregnancy has still to be more completely evaluated.

SUMMARY

The published results obtained with relaxin in obstetric indications are reviewed.

Other investigational work in progress is mentioned and described.

Correlation between laboratory findings and clinical observations is indicated.

Results obtained in the treatment of scleroderma are described.

Other possible uses for relaxin are suggested.

The place of relaxin in the hormonal triumvirate of pregnancy is indicated and its possible action as a uterine anodyne is mentioned.

REFERENCES

1. HISAW, F. L.: *Proc. Soc. Exper. Biol. & Med.*, **23**: 661, 1927.
2. ZARROW, M. X., HOLMSTROM, E. G. AND SALHANICK, H. A.: *J. Clin. Endocrinol.*, **15**: 22, 1955.
3. GRAHAM, E. F. AND DRACY, A. E.: *J. Dairy Sc.*, **36**: 772, 1953.
4. ZARROW, M. X., SIKES, D. AND NEHEN, G. M.: *Am. J. Physiol.*, **179**: 687, 1954 (abstract).
5. ZARROW, M. X. AND BRENNAN, D. M.: The Effect of Relaxin on the Concentration of Water in the Uterine Tissue of the Rat. Communications, 20th International Physiological Congress. Brussels, Belgium, July 30-Aug. 4, 1956, p. 990.
6. STEINETZ, B. G., BEACH, V. L. AND KROC, R. L.: *Endocrinology*, **61**: 271, 1957.
7. DRACY, A. E.: Personal communication, January 1957.
8. SANDS, R. X.: Current Status of Relaxin, *West. J. Surg. Obst. & Gynec.* Accepted for publication, 1958.
9. STONE, M. L., SEDLIS, A. AND ZUCKERMAN, M. B.: Relaxin —Critical Evaluation. *Am. J. Obst. & Gynec.* Accepted for publication, 1957.
10. MACLURE, J. G.: *Bull. Univ. Miami School Med.*, **11**: 45, 1957.
11. FERGUSON, J. H. AND MACLURE, J. G.: Personal communication, Miami, March 1957.
12. BIRNBERG, C. H. AND ABITOL, M. M.: *Obst. & Gynec.*, **10**: 366, 1957.
13. KO, J. AND JAVERT, C. T.: Woman's Hosp. (N.Y.C.), personal communication.
14. KASDEN, S. C. AND FRIEDEN, E. H.: The Effects of Relaxin Containing Preparations upon the Pregnant Human Uterus. Presented at the 39th Annual Meeting of the Endocrine Society, New York, May 30, 1957.
15. MCGAUGHEY, H. S., JR., COREY, E. L. AND THORNTON, W. N., JR.: *Am. J. Obst. & Gynec.*, **75**: 23, 1958.
16. KELLY, J. V. AND POSSE, N.: *Obst. & Gynec.*, **8**: 531, 1956.
17. ABRAMSON, D. AND REID, D. E.: *J. Clin. Endocrinol.*, **15**: 206, 1955.
18. EICHNER, E. *et al.*: *Am. J. Obst. & Gynec.*, **71**: 1035, 1956.
19. FOLSOME, C. E. *et al.*: *Obst. & Gynec.*, **8**: 536, 1956.
20. MCCARTHY, J. J., JR., ERVING, H. W. AND LAUFE, L. E.: *Am. J. Obst. & Gynec.*, **74**: 134, 1957.
21. BOUCEK, R. J.: Lectures on Orthopedics and Rheumatic Diseases, Dedication Volume (Hospital for Special Surgery), September 1955.
22. CASTEN, G. G. *et al.*: *Am. J. Med.*, **20**: 943, 1956 (abstract)
23. CASTEN, G. G. AND BOUCEK, R. J.: *J. A. M. A.*, **166**: 319, 1958.
24. EVANS, J. A. AND FROMER, J. L.: Releasin Therapy in Diffuse Progressive Scleroderma, prepared for publication, February 1958.
25. BOUCEK, R. J. *et al.*: Effects of Relaxin on Connective Tissue. Read by invitation at the 15th Annual Meeting of the American Academy of Dermatology and Syphilology, Chicago, December 8, 1956.
26. MOLANDER, D. W. AND SANDS, R. X.: *Clin. Research*, **6**: 146, 1958 (abstract).
27. NOBLE, N. L. AND BOUCEK, R. J.: *Circulation Res.*, **5**: 573, 1957.
28. POSSE, N. AND KELLY, J. V.: *Gynec. & Obst.*, **103**: 687, 1956.
29. LARKIN, W.: Personal communication, December 1957.

RÉSUMÉ

La relaxine est une hormone qui favorise le relâchement des articulations du bassin chez plusieurs espèces de mammifères au cours de la mise à bas. On l'a extraite jusqu'à présent des ovaires de truies gravides, et le produit est évalué en unités de cobaye. Sa structure chimique est celle d'une protéïne ou d'un polypeptide mais non d'un stéroïde. Elle apparaît dans le sérum de la femme enceinte augmente en concentration au cours de la grossesse jusqu'à l'accouchement et disparaît dans les 24 heures qui suivent. Une bonne partie de l'expérimentation animale de cette hormone a été faite jusqu'ici dans le domaine vétérinaire. On a remarqué qu'elle augmente la teneur de l'utérus en eau et en glycogène chez l'animal. Au point de vue clinique son administration par voie intraveineuse suivie de pitocine a donné des résultats prometteurs dans les cas où le travail s'annonçait difficile à cause de la conformation du col. On a noté qu'elle abrège la durée du travail, relâche le périnée et diminue les douleurs de l'accouchement. On prétend cependant dans certains milieux qu'elle peut inhiber les contractions utérines; cette opinion n'est pas partagée par tous les auteurs. On a cherché à appliquer ses propriétés relâchantes à des domaines extragénitaux; c'est ainsi qu'on l'a administrée dans la sclérodermie avec certain succès. On est à déterminer sa valeur dans les états qui produisent la fibrose que ce soit dans le foie, la cornée ou les cicatrices. Certains auteurs ont même prétendu qu'elle diminue la synthèse du cholestérol dans le tissu conjonctif. Sa toxicité serait très basse.

CARTOONS

Readers may have observed that on page 907 of the June 1 issue and on page 37 of this issue a cartoon has been added to the usual features of the Journal. We are often urged to introduce a note of humour; we hope that both our physician readers and their wives will like this first step towards fulfilling this want.

Case Reports

MALIGNANT OVARIAN NEOPLASMS COMPLICATING PREGNANCY* REPORT OF TWO CASES

ALLAN DAY, M.B.,† and
D. J. MURRAY, B.Sc., M.D.,‡
Edmonton, Alta.

THE EXTREMELY INFREQUENT occurrence of malignant neoplasms of the ovaries complicating pregnancy has prompted the writers to report their experience in 13 years, in the private practice of the senior author and his associate, Dr. D. C. Ritchie, in a review of 8429 pregnancies.

INCIDENCE

The incidence of ovarian neoplastic tumours complicating pregnancy as quoted by several authors varies considerably. Gustafson[1] in 1954 reported 45 surgically proven ovarian tumours of 6 cm. diameter or larger from a group in excess of 100,000 pregnancies. However, this group contained four corpus luteum cysts, two parovarian cysts, two endometrial cysts and one case of œdema of the ovary. If these nine cases were removed, it would leave 36 cases of true ovarian neoplasms, an incidence of 0.036%, or one in 702. In the group studied, the incidence varied in the different hospitals from 1:1000 to 1:8000. Of these tumours, two were malignant, which would give a percentage rate for malignancy of 5.5.

The figure of 0.1% or less of pregnancies having complicating ovarian neoplasms is quoted by Bossert,[2] who found malignancy in 5-7% of the cases reviewed. In addition to his reported case of bilateral ovarian carcinoma complicating pregnancy, he reviewed 14 cases of ovarian malignancy complicating pregnancy, and also referred to an earlier publication of Szathmary in 1933 in which 39 cases were presented. However, in the opinion of several authors these were rather poorly documented.

Dougherty and Lund[3] reviewed the reported cases of solid ovarian tumours over a 15-year period. Of 30 cases, eight were malignant, namely, four Krukenberg tumours, one solid adenocarcinoma and three sarcomas. Hamilton and Higgins[4] quote McKerran's figure of 5% malignancy in ovarian neoplasms complicating pregnancy. Hass[5] in a review of adnexal cysts complicating pregnancy found 10 cases of neoplastic tumours over a 13-year period in 7598 pregnancies, giving a percentage rate of 0.131. It will be seen that our figures presented here are very close to those of Hass. However, he also had 15 other cases of non-neoplastic cysts, nine of which were not operated upon.

TABLE I.—OVARIAN NEOPLASMS COMPLICATING PREGNANCY—12 CASES

Type of tumour	*Age*	*Parity* Para.	Gravida	*When detected*	*Time of operation*	*Method of delivery*	*Size of tumour*
				Gestation			
Serous cystadenoma (L)	32	1	2	12 weeks	19 weeks	Spontaneous 40 weeks	10 cm.
Serous cystadenoma (L)	26	1	2	7 "	17 "	Spontaneous 41 weeks	14 cm.
Serous cystadenoma (R)	26	1	2	15 "	17 "	Spontaneous 41 weeks	8 cm.
Benign teratoma (L)	25	0	1	10 "	36 "	Cæsarean and removal (impacted)	11 cm.
Benign teratoma (R)	28	0	1	12 "	21 "	Spontaneous 41 weeks	8 cm.
Benign teratoma (R)	36	2	3	9 "	14 "	Spontaneous macerated 33 weeks	12 cm.
Benign teratoma (R)	26	0	1	8 "	10 "	Spontaneous delivered 40 weeks	10 cm.
Benign teratoma (R)	26	1	2	9 "	19 "	Spontaneous delivered 38 weeks	6 cm.
Benign teratoma (L)	27	0	1	7 "	17 "	Forceps delivered 43 weeks	7 cm.
Benign teratoma (L)	19	0	1	11 "	18 "	Spontaneous delivered 40 weeks	8 cm.
Serous cystadeno-carcinoma (L)	36	2	5	24 "	24½ "	Cæsarean hysterectomy and bilateral oophorectomy	15 cm.
Bilateral Krukenberg	41	4	5	20 "	21 "	Cæsarean hysterectomy and bilateral oophorectomy	15 cm.

In our present review of 8429 cases, we encountered 15 cases which were ultimately operated upon, though one proved to be a corpus luteum cyst 7 cm. in diameter, which when excised at 14 weeks' gestation had the appearance of a simple unilocular cyst. The patient, who had been seen in consultation on three occasions, went on to term. Two other cases encountered late in pregnancy were not operated upon until four and six months post partum. One of the tumours was a serous cystadenoma and the other a benign teratoma. These last three cases are not included in our list of documented cases, which leaves 12 cases of ovarian neoplasms complicating pregnancy.

Of these 12 tumours, three were serous cystadenomas, seven unilateral benign teratomas, one

*Presented at the meeting of the Pacific Northwestern Obstetrical and Gynecological Society, Sun Valley, Idaho, May 24, 1957.

†Royal Alexandra Hospital, Edmonton, Alberta.
‡Department of Pathology, Royal Alexandra Hospital, Edmonton, Alberta.

Canad. M. A. J.
June 15, 1958, vol. 78

was a unilateral serous cystadenocarcinoma, and one a bilateral Krukenberg tumour. This gives an incidence of 0.14% of ovarian tumours complicating pregnancy in our series; of these, two were malignant—an incidence of 16.06%.

CASE 1.—*Krukenberg tumour of ovaries complicating a pregnancy of from four to five months' duration.* Mrs. D.H., white, aged 41 years, para. IV, gravida V, was admitted to the Royal Alexandra Hospital on January 7, 1956. On admission, she complained of nervousness and headaches for two years, abdominal distension of three weeks' duration, and dyspnœa and amenorrhœa for four months. During the previous six months she had lost 20 lb. Past and family history were non-contributory.

Physical examination on admission revealed a well-nourished, highly nervous, apprehensive patient, perspiring profusely. Blood pressure was 200/100 mm. Hg; pulse rate 120. The skin was moist and there was a fine tremor of the hands. The chest appeared clear and the heart sounds were normal. The abdomen was larger than was commensurate with the period of gestation. Pelvic examination revealed the uterus to be enlarged, and the cervix soft and displaced anteriorly by a large mass in the pouch of Douglas. Ballottement could not be elicited, but in view of a positive Hogben frog test before admission she was thought to be pregnant, though two further biological tests were negative. *Other laboratory findings*: Urine was not abnormal. The white blood cell count was 11,800/c.mm. with 76% neutrophils and 24% lymphocytes; hæmoglobin 13.6 g. %, hæmatocrit 43% and erythrocyte sedimentation rate 45 mm. in one hour; the basal metabolic rate was plus 58 on January 10 and plus 69 on January 13; serum cholesterol 345 mg. %, 268 mg. % and 296 mg. % on various occasions. The radioactive iodine conversion ratio was 14.7%. It was thought that several cholecystograms taken some time previously might have affected this reading. A radiograph of the abdomen showed a faint outline of a fetus and a suggestion of a pelvic tumour. The clinical impression was one of pregnancy complicated by hyperthyroidism and a large ovarian tumour, possibly a struma ovarii.

The patient was given sedatives and Lugol's iodine. Since her condition was not improving, it was felt that laparotomy should not be postponed any longer and the operation was performed on January 18, 1956. Approximately one and one-half gallons of fluid were evacuated. The uterus was about the size of a five-month pregnancy. Exploration of the pelvis revealed two large non-adherent ovarian neoplasms. A hysterotomy was performed, followed by the removal of both tumours and a hysterectomy. No abdominal metastases were found nor was there evidence of the primary growth at this time.

Pathological description: The tumours were quite symmetrical and weighed over 500 g. each. The serosal surface was smooth and somewhat lobulated, with a few small nodules present close to the tubal margin. They each measured 15 cm. in diameter, and on cross section were solid and slightly nodular.

Microscopically, the sections showed a typical clear cell carcinoma of the Krukenberg type. The individual cells were circular with signet ring nuclei and numerous mitotic divisions. Approximately 30 sections from both ovaries showed a uniform histological pattern.

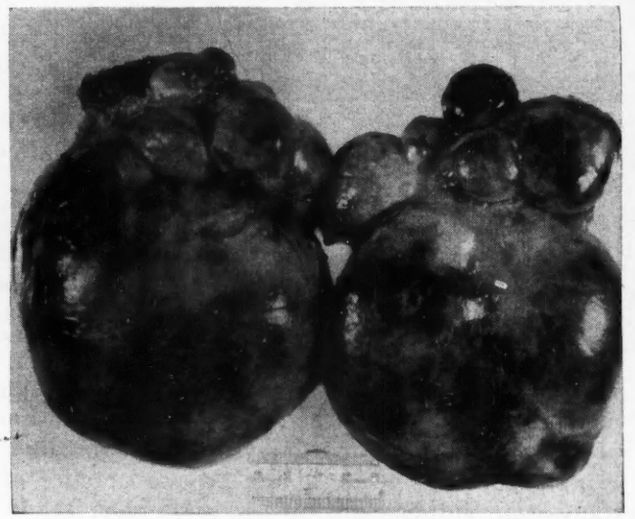


Fig. 1 (Case 1).—External appearance of one of the Krukenberg tumours of the ovary. The other tumour was of similar appearance.

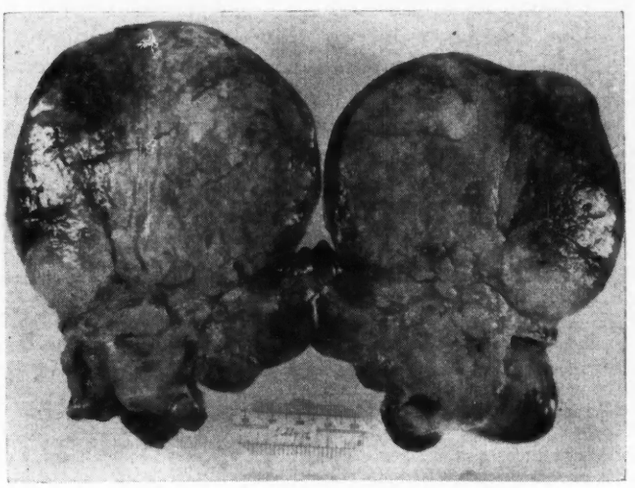


Fig. 2.—Cross-section of the tumour in Fig. 1.

Pathological diagnosis: (1) Bilateral carcinoma of ovaries of the Krukenberg type; (2) gravid uterus—approximately 4-5 months' gestation.

This case fulfils all the criteria set forth by Novak[7] for such a tumour.

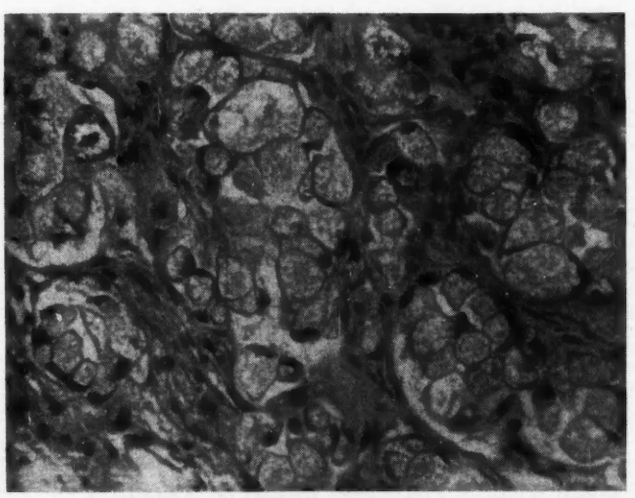


Fig. 3.—Characteristic histologic section of the Krukenberg tumour showing the multiple "signet ring cells". ×600.

The day before discharge, January 31, the patient's B.M.R. was plus 6. She returned to hospital again three and one-half months later, on May 14, 1956, with vomiting. Intestinal obstruction being suspected, she was operated upon by a general surgeon who found general carcinomatosis but no primary lesion and no obstruction. She was again discharged on June 2, 1956, and died at home soon after. No postmortem examination was obtained, since the patient lived 100 miles north of Edmonton.

CASE 2.—*Serous cystadenocarcinoma of the left ovary complicating a pregnancy of 5 months' duration.* Mrs. A. J., aged 37, white, para. II, gravida V, first reported to the office on August 28, 1956. At that time she gave a history of some bleeding; her last normal period had been on May 5, 1956. No pelvic examination was done at that time, but the cervix was inspected and marked cervicitis with bleeding was noted. Silver nitrate was applied. The size of the uterus was commensurate with the period of amenorrhœa. Apart from some headache and dizziness, her complaints then were negligible.

Fig. 4 (Case 2).—Gross appearance of the uterus and adnexæ. Cystic ovary is opened to show the papillary tumour mass in the case of serous cystadenocarcinoma of the ovary.

At return visits to the office on September 5 and 26, 1956, no bleeding was seen. However, on October 15, 1956, a pelvic examination was performed because of pain in the back and lower abdomen. A mass in the cul-de-sac was felt which pushed the uterus and cervix forward. This was considered to be either a pedunculated fibroid or a solid ovarian tumour.

The patient was admitted to hospital on October 15 for examination under anæsthesia and possible laparotomy. Radiography revealed a fetal skeleton in the right mid-abdomen but no evidence of tumour. Examination under anæsthesia revealed a large conical mass about 8-10 cm. long and 5-6 cm. in diameter, adherent to the left side of the pelvis and to the vault of the vagina. It was firm and nodular with no evidence of fluctuation; a diagnosis of ovarian tumour or fibroid was entertained. Laparotomy was performed and a large cystic mass on the left side approximately 12 cm. long, and adherent to the side wall of the pelvis, the sigmoid and the posterior aspect of the uterus, was encountered. The lower pole of this mass involved the posterior aspect of the vagina and was quite solid. The right adnexa appeared normal. As the growth was considered malignant, a hysterotomy, followed by hysterectomy and bilateral salpingo-oophorectomy, was performed with removal of a wide cuff of the vagina.

Pathological description: The uterus measured 14 cm. in length, and the ovarian mass, both cystic and

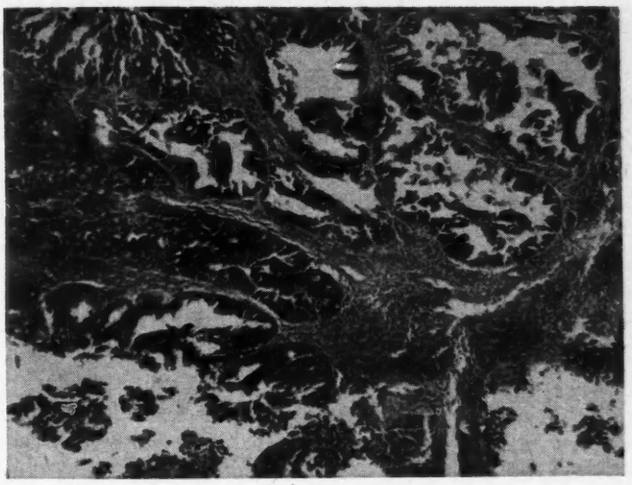


Fig. 5.—Microscopic section of the serous cystadenocarcinoma. ×300.

solid, measured 15 cm. in length. The contents of this cystic mass consisted of a large mass of cauliflower-like material. Microscopic sections from the ovarian tumour showed it to be a serous cystadenocarcinoma composed of poorly defined papillary projections covered by epithelial cells irregularly polyhedral in outline with hyperchromatic basophilic nuclei and a large amount of pale basophilic cytoplasm. Many mitotic figures were present and the tumour in a few areas was seen growing in solid sheets. No secondary tumour was seen in any of the other tissues.

The patient was discharged on the 12th postoperative day, with a diagnosis of pregnancy of five months' duration complicated by serous cyst adenocarcinoma of the left ovary.

After her discharge from hospital she was sent to the Cancer Clinic where it was noted that some ascitic fluid was draining through the vault of the vagina. She received Co^{60} therapy from November 8 to December 6, 1956, through two opposing 15 cm. x 15 cm. fields; separation between these fields was 17 cm. Twenty treatments were given. It is estimated that an average dose in the midplane of 5000 r was delivered with a skin dose of 5260 r. Pelvic examination on March 22, 1956, revealed some thickening in the region of the uterosacral ligaments but no masses were palpated.

DISCUSSION

Burke[6] in 1953 reported a case of Krukenberg tumour of the ovaries complicating a 32-weeks' pregnancy. He refers to five cases reported in the literature, of which only two exceeded 28 weeks' gestation. In their review in 1954 Gustafson, Gardiner and Stout published one case of Krukenberg tumour discovered in the sixth month of pregnancy, which, as stated before, was from a group in excess of 100,000 pregnancies. Four cases of this type were noted by Dougherty and Lund in their review. These were all discovered before the 28th week of pregnancy. Several reports of primary carcinoma of the ovary complicating pregnancy were found. Dougherty and Lund in their review include one case of solid cystadenocarcinoma originally reported by Bossert. Of May's three cases, two were serous cyst-

Canad. M. A. J.
June 15, 1958, vol. 78

adenocarcinomas with massive lymph node involvement at three and five months' gestation respectively. In his case of pseudomucinous cystadenocarcinoma, removed at term, the tumour appeared confined to the ovary and the patient was alive and well five years later.

Hamilton and Higgins reported the case of two patients with papillary cystadenocarcinoma treated by excision of the tumour at 12 and 14 weeks' gestation with apparent cure. In one case of solid carcinoma the patient was treated by oophorectomy with postoperative radiation therapy and died eight months later of metastases.

A Grade II adenocarcinoma of the ovary removed at 14 weeks' gestation was reported by Gustafson. The patient later underwent Cæsarean hysterectomy and right salpingo-oophorectomy near term. She was well five years after operation.

SUMMARY

The histories of over 8000 pregnancies managed in private practice over a 13-year period have been carefully reviewed. In this series we encountered 12 cases of ovarian neoplasms complicating pregnancy, two of which were malignant. One of these was a case of Krukenberg's tumour of the ovaries which was of extreme interest because of the complicating thyrotoxicosis. The other was a case of unilateral serous cystadenocarcinoma of the ovary. A review of the more recent reports of ovarian malignancy complicating pregnancy is presented.

CONCLUSION

It would appear from a review of the literature on this subject that the statistics for incidence of neoplastic growths complicating pregnancy are very variable, with a range of 1:1000 to 1:10,000 cases. We are not prepared to explain this, except to say that patients encountered in private practice may be seen earlier and more often than those in large clinics, so that cases are discovered more frequently.

We were unable to find the number of functional cysts encountered in the series reviewed, but by and large we do not think this offers too much of a diagnostic problem, as only one was removed in this series.

Benign teratomas were greatly in the majority in the non-malignant neoplasms—in a proportion greater than 2:1 as compared to serous cystadenomas.

Searching pelvic examination of all patients when they first report is advised. In this small series, with the exception of the serous cystadenocarcinoma, all neoplasms were detected at the first visit.

All ovarian neoplasms of 6 cm. diameter or over should with few exceptions be removed as soon as possible. Delay is not justified.

We are indebted to Dr. P. Davey, Pathologist, Royal Alexandra Hospital, for his review of old slides and his preparation of the slides for presentation.

REFERENCES

1. GUSTAFSON, G. W., GARDINER, S. H. AND STOUT, F. E.: *Am. J. Obst. & Gynec.*, 67: 1210, 1954.
2. BOSSERT, L. J.: *Ibid.*, 44: 336, 1942.
3. DOUGHERTY, C. M. AND LUND, C. J.: *Ibid.*, 60: 261, 1950.
4. HAMILTON, H. G. AND HIGGINS, R. S.: *Surg. Gynec. & Obst. (I.A.S.)*, 89: 525, 1949.
5. HASS, R. L.: *Am. J. Obst. & Gynec.*, 58: 283, 1949.
6. BURKE, S.: *J. Obst. & Gynæc. Brit. Emp.*, 60: 915, 1953.
7. NOVAK, E. AND NOVAK, E. R.: Gynecologic and obstetric pathology, with clinical and endocrine relations, 4th ed., W. B Saunders Company, Philadelphia, 1958.
8. WAY, S. A.: Malignant disease of the female genital tract, J. & A. Churchill, Ltd., London, 1951.

SUPERINFECTION AND SYSTEMIC MONILIASIS

S. ADRIAN YAFFE, M.D., M.R.C.P.(Lond.),
Hamilton, Ont.

SINCE THE ADVENT of the first sulfonamides in 1935, we have gradually grown to feel that we can conquer most infections. During World War II, when sulfonamides were used prophylactically to control infection of battle casualties, the presence of bacterial resistance to these drugs was noted, but the emergence of penicillin in 1943 served to control to some degree this poorly explained occurrence.

There have been a host of new antibiotics since then, and even though their expense originally limited their use, it is now becoming apparent that the public insist on these drugs regardless of cost in the treatment of minor infections, and others in which they are not even effective.

During the past few years, we have gradually become aware of a new condition called *superinfection*. The word has a double meaning, since there is a superimposed infection on the one hand, and also a *super* infection in the sense that the infection is perhaps uncontrollable and fatal. During the past few years, there have been an increasing number of reports of fungus infections in the literature. It is true that occasional fungal infection was observed in the past, but it has been shown that in some conditions, particularly leukæmia and lymphomas, moniliasis was not a complication before the antibiotic age.

Benham and Hopkins[1] (1933) showed that *Monilia* (*Candida*) *albicans* was present in at least 3% of normal rectums. Todd[3] (1937) reported monilia in 14% of 1000 throats of healthy adults. Harris[2] (1950) reported mucocutaneous complications of treatment with aureomycin and chloramphenicol, due to *Candida albicans*. Zimmerman[4] (1950) reported three fatal cases of fungal endocarditis. Woods, Manning and Patterson[5] (1951), Gausewitz, Jones and Worley[6] (1951), Keefer[7] (1951), Smith[8] (1952), Kligman[9] (1952), and others have suggested that *Candida albicans* rapidly develops in the mouth and gastro-intestinal tract of those receiving wide-spectrum antibiotics. Brown *et al.* (1953) reported five fatal cases of moniliasis following intensive antibiotic therapy. Sharp[10] (1954) showed that monilia did not increase during sulfonamide therapy, but after completion of treatment this fungus increased in the

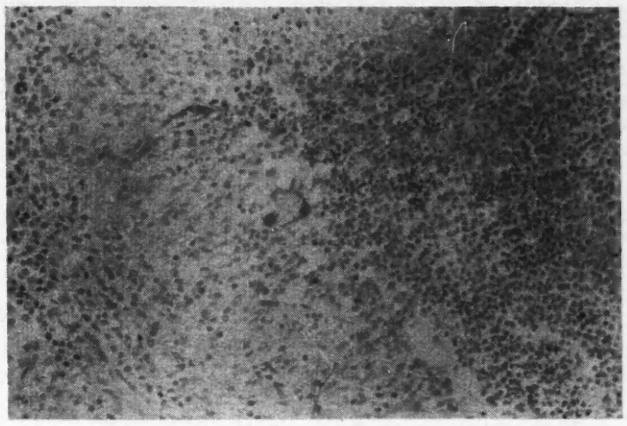


Fig. 1.—Section of spleen, showing monilial granuloma.

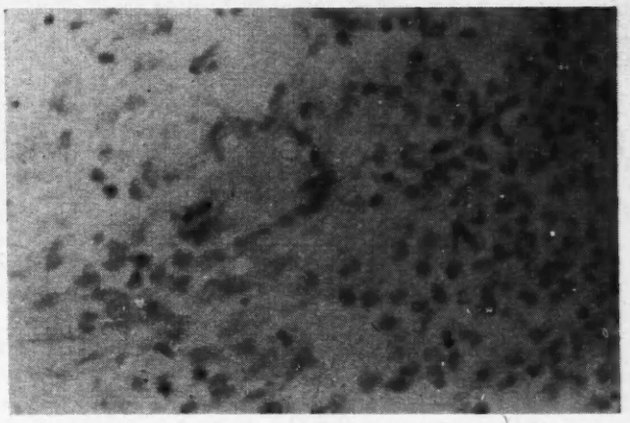


Fig. 2.—Section of spleen — high power view of same section.

sputum from 30 to 49%, and in the rectum from 5 to 20%. With terramycin, there was a significant increase of monilia during therapy. Browne[11] (1954) reported bronchomoniliasis after 6.5 mega units of penicillin. Bass, MacFarlane and Phillips[12] (1954) reported bilateral hæmorrhagic effusions complicating acute pulmonary moniliasis. However, Warr[13] (1931) and Koerth, Donaldson and McCorkle[14] (1941) have also described similar pleural effusions before the advent of wide-spectrum antibiotics.

We are thus faced with an increasing dilemma. When should the presence of *Monilia albicans* be regarded as proof that it is the offending pathogen? In most instances, it is probably merely vegetating on the affected mucous membrane. However, the circumstances which may change it into a pathogenic agent remain undetermined. When the fungus is found in a fibrinous matrix of freshly expectorated membrane, or in ulcerative lesions of the mouth or the œsophagus or skin, the diagnosis is no longer in doubt.

A middle-aged woman had had agranulocytosis for 14 years. She developed a sinusitis in March 1955, and was treated with penicillin at home. After a week, her fever returned and was associated with a spasmodic cough and chills and pneumonia at one base. On admission to hospital she had a white cell count of 1200 and no neutrophils. She was treated with multiple antibiotics and corticosteroids, which restored her neutrophil count to active levels. Sputum contained a mixed flora which was sensitive to chloramphenicol and erythromycin, and she was continued on these drugs for several weeks. Her pneumonia resolved slowly, but her fever was remittent and her white cell count was difficult to judge because of the corticosteroids. She developed some ulcerative lesions in her mouth (treated with gentian violet) and had difficulty in swallowing. It was assumed that she had an œsophageal ulcer as well, and she was fed by gastric tube for about 10 days because intravenous therapy had ruined most of her veins. After removal of the tube, she vomited most foods, had an associated spasmodic cough and glairy mucoid sputum, and lived mainly on fluids. She had a dirty vaginal discharge and a crural rash; she was bodily placed in a tub bath daily, and these lesions gradually subsided.

She had a past history of arthritis with recurrent exacerbations, and also of treatment with sulfonamide for a kidney infection. It was considered that she was suffering from Felty's syndrome, which would account for her agranulocytosis. It was decided to remove her spleen.

At operation, fungating white nodules were noted in her liver and spleen. On section (Figs. 1, 2, 3 and 4) and culture of the spleen *Monilia albicans* was found. Subsequent cultures of throat, sputum and fæces also showed *Monilia albicans*. This was thus a case of systemic moniliasis.

At a joint C.M.A.-B.M.A. (1955) meeting, I discussed this case with a panel of speakers on chemo-

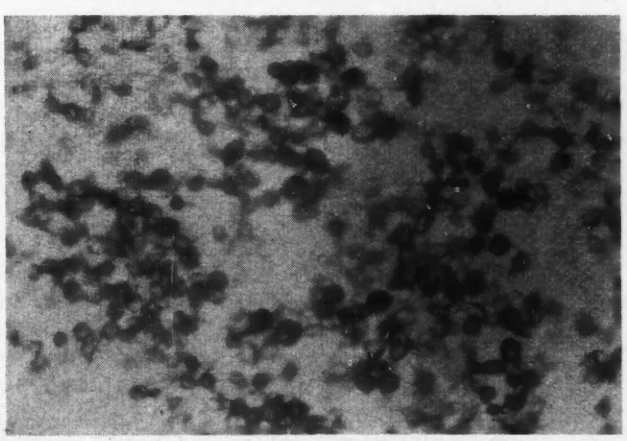


Fig. 3.—Section of spleen—hæmatoxylin and eosin stain showing monilia.

Fig. 4.—Section of spleen—special silver stain to show monilia.

Canad. M. A. J.
June 15, 1958, vol. 78

therapy, but apart from the use of potassium iodide, which she had already been given, they had no suggestion.

About this time, nystatin (Mycostatin) was introduced. I obtained a supply for experimental trial of parenteral therapy, since it is not absorbed through the gut. With the assistance of our pharmacist, Mr. Foultis, the drug was dissolved in propyl alcohol and given intraperitoneally and intramuscularly for one week. The patient developed gluteal abcesses which resolved with local measures. Cultures, however, gradually became negative and have stayed negative.

She continued to vomit and had a spasmodic cough, and gastro-intestinal studies were negative. After repeated difficulties for some weeks, a barium swallow showed a diverticulum of the œsophagus and spasm. Two œsophagoscopies revealed only some slight inflammatory reaction and no constriction of the lumen. Because of the marked spasm, however, the œsophagus was dilated with bougies; the condition was only partially helped. She also had recurrent bouts of bronchitis with coarse rales at the lung bases; bacteriological studies again showed a mixed flora of alpha hæmolytic streptococci, non-hæmolytic *Staph. aureus* and *Aerobacter aerogenes*. She was treated with blow-bottles, and after several weeks her cough resolved and did not recur.

There have been similar reports in the literature of dysphagia associated with moniliasis.

DISCUSSION

This case fits the pattern of superinfection with monilia, associated with prolonged use of antibiotics. The diagnosis of such a complication is difficult. The clinical picture of systemic moniliasis is not clear-cut. In retrospect, there were fever, sweats, weakness, malaise, buccal ulcers, dysphagia, spasmodic cough, abdominal pains, vaginal discharge and marked toxicity. These are all general symptoms, and may be found in any infection. We are too used to thinking in terms of pyogenic infections and ordinary cultures and sensitivity tests to choose a suitable antibiotic. In prolonged febrile states, where antibiotics have been used, it would seem advisable to think also in terms of fungi and to order special cultures to identify them.

This patient originally had agranulocytosis and, though cortisone improved this picture, these steroids act particularly on the granulocytes. Hence one cannot say whether the raised white cell count and high neutrophil count were not due to drugs rather than to moniliasis.

The remarkable results of nystatin in resolving such a widespread lesion represent an important stride in therapy. The difficulty of providing parenteral therapy with an insoluble salt will probably be overcome. The sterile abscesses this patient developed resolved, but did aggravate her discomfort.

SUMMARY

A case of systemic moniliasis is reported. The association of debility and wide-spectrum antibiotics probably plays a part in the pathogenicity of moniliasis. The use of nystatin (Mycostatin) proved effective therapy.

I am indebted to Dr. John Lynch, assistant pathologist at Hamilton General Hospital, for the sections and photographs. The supplies of nystatin (Mycostatin) were kindly given to me by E. R. Squibb & Sons of Canada Limited.

REFERENCES

1. BENHAM, R. W. AND HOPKINS, A. M.: *Arch. Dermat. & Syph.*, 28: 532, 1933.
2. HARRIS, H. J.: *J. A. M. A.*, 142: 161, 1950.
3. TODD, R. L.: *Am. J. Hyg.*, 25: 212, 1937.
4. ZIMMERMAN, L. E.: *Arch. Path.*, 50: 591, 1950.
5. WOODS, J. W., MANNING, I. H., JR. AND PATTERSON, C. N.: *J. A. M. A.*, 145: 207, 1951.
6. GAUSEWITZ, P. L., JONES, F. S. AND WORLEY, G., JR.: *Am. J. Clin. Path.*, 21: 41, 1951.
7. KEEFER, C. S.: *Am. J. Med.*, 11: 665, 1951.
8. SMITH, D. T.: *Ann. Int. Med.*, 37: 1135, 1952.
9. KLIGMAN, A. M.: *J. A. M. A.*, 149: 979, 1952.
10. SHARP, J. L.: *Lancet*, 1: 390, 1954.
11. BROWNE, S. G.: *Ibid.*, 1: 393, 1954.
12. BASS, B. H., MACFARLANE, R. G. AND PHILLIPS, T.: *Ibid.*, 1: 709, 1954.
13. WARR, O. W.: *Ann. Int. Med.*, 5: 307, 1931.
14. KOERTH, C. J., DONALDSON, J. M., JR. AND MCCORKLE, R. G.: *Am. Rev. Tuberc.*, 43: 723, 1941.
15. VON OETTINGEN, W. F.: *Am. J. Med.*, 18: 792, 1955.

Medical Arts Building,
Hamilton, Ontario.

LIPOMA (LIPOMATOUS HAMARTOMA) OF DORSAL MIDBRAIN

MURRAY R. ABELL, M.D., Ph.D.,* *Ann Arbor, Mich.*,
and DOUGLAS M. MILLS, M.D.,† *Windsor, Ont.*

LIPOMATOUS TUMOURS of the brain are uncommon lesions and when they are found in the region of the dorsal midbrain, they may be classed as rarities. They are of interest not only because of their infrequent occurrence, but also because of the many theories that have been advanced to explain their genesis.

Most of the lipomas that have been reported were small and symptomless, and were discovered incidentally at necropsy. Vonderahe and Niemer[1] found four intracranial lipomas, none of which was suspected clinically, in 5000 necropsies. Three of the lipomas were described as approximately the size of peas. Very few lipomas have become sufficiently large to produce signs and symptoms of an expanding intracranial lesion.[2, 3]

Bailey and Bucy,[3] in 1931, found "some sixty" cases of intracranial lipomas recorded in the literature. Four of these were located in the region of the corpora quadrigemina. They reported the fifth lipoma in this location. In 1936 Sperling and Alpers[2] reported a large lipoma of the third ventricle and in a review of the literature collected 74 cases of cerebral lipoma or osteolipoma. Ehni and Adson[4] (1945) accepted only 69 recorded examples of

*Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.
†Department of Pathology, Hôtel-Dieu of St. Joseph, Windsor, Ontario.

lipoma of the brain. They reported two additional cases, one of which they believed to be the first to be removed surgically. Ewing,[5] however, referred to an intracranial lipoma which was excised by Weil in 1890. Ehni and Adson[4] listed four common sites of intracranial lipomas in order of frequency as—corpus callosum, the ventral diencephalic structures, the choroid plexus or the ventricular walls of the lateral and third ventricles, and, finally, the dorsal aspect of the midbrain.

List, Holt and Everett[6] in 1946 collected 28 reports of lipomas of the corpus callosum and added two cases. To their series, Nordin, Tesluk, and Jones[7] (1955) added 14 cases from the literature and one of their own. Barber[8] (1950) reviewed the literature and reported the eleventh solitary lipoma of the choroid plexus. She referred to six additional cases in the literature accompanied by lipomas in other locations throughout the central nervous system. Ehni and Adson[4] stated that seven lipomas had been reported in the region of the dorsal midbrain. They did not apparently include the second case of Vonderahe and Niemer.[1] No additional reports of similarly located lipomas have been found, so that the following case would appear to be the ninth recorded lipoma of the dorsal midbrain.

History.—The patient, a 25-year-old white male, was involved in a relatively minor automobile accident (damage to his vehicle was assessed at between $100 and $200). Death, however, occurred almost instantaneously and was attributed to multiple skull fractures and cerebral lacerations.

The victim's past history was obtained from his brother, who knew of no significant illness during the patient's childhood or early adult life but stated that his brother's head had been larger than normal as long as he could remember. He recalled that, as a child, his brother wore his father's caps, which fitted perfectly. The patient attended public school and three years of high school. He obtained grades above average. His employment required better than average intelligence, and attendance was good. For about one year before his death, the patient complained of severe intermittent headaches which frequently awakened him at night. He had expressed the feeling that there had been some further enlargement of his head.

Gross observations at necropsy.—Necropsy was performed nine hours after death. The body was well developed, weighed approximately 180 lb., and measured 73 inches (1.83 m.) in length. There were superficial abrasions of the forehead and scalp and a subcutaneous hæmatoma of the right side of the face and neck. The head was large. With the exception of left ventricular cardiac hypertrophy and bilateral pulmonary œdema, the positive findings were limited to the scalp, skull and brain. There were numerous stellate fractures of the vault of the skull, which was very thin. Beneath the aponeurosis of the left side of the scalp, there was a large hæmatoma which contained small fragments of bone and cerebral tissue. The left cerebral hemisphere was badly lacerated. The cerebral convolutions were flat and the sulci shallow.

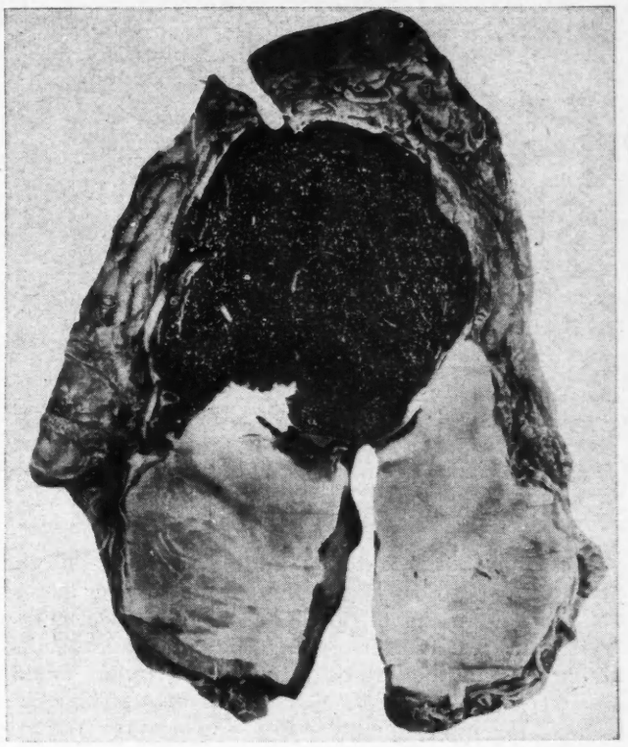


Fig. 1.—Lipoma of dorsal midbrain stained with Sudan IV. The tumour has infiltrated the brain and pushed the ependyma inward.

During removal, the brain ruptured, allowing escape of a large amount of cerebrospinal fluid. The lateral ventricles were markedly dilated and the cerebral cortex was very thin.

There was an oval-shaped tumour involving the dorsal portion of the midbrain (Fig. 1). The tumour was intimately connected with the pia mater and covered by adherent arachnoid. It measured 3.1 by 2.6 by 2.0 cm. and was partially encapsulated. There was no connection with the corpus callosum and the pineal body appeared normal. The cut surface presented a greasy yellow appearance and absorbed Sudan IV readily (Fig. 1), indicating its lipomatous nature. The mass appeared to infiltrate the tectum of the midbrain. A small portion of tumour projected into the ventricular system and almost occluded the opening of the aqueduct into the fourth ventricle. The aqueduct also was distorted by the tumour.

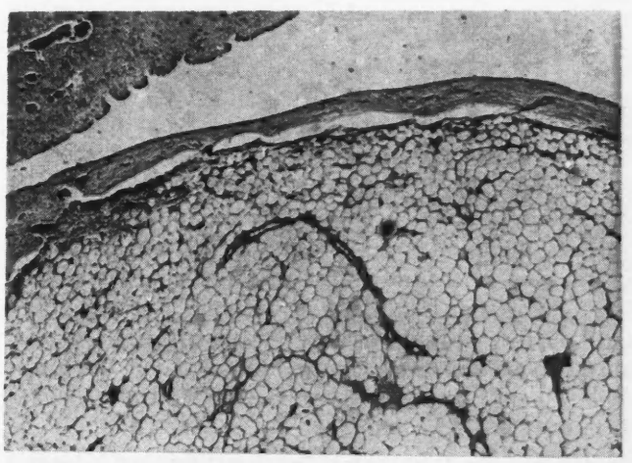


Fig. 2.—Mature adipose tissue of the tumour separated from the ependyma by a thin zone of glial tissue. (Hæmalum and eosin stain: ×75.)

Canad. M. A. J.
June 15, 1958, vol. 78

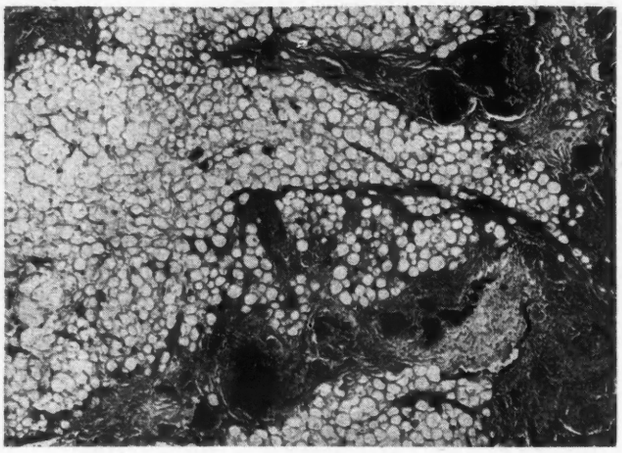


Fig. 3.—Glial tissue and nerve fibres of the midbrain incorporated in the lipomatous mass. The black irregular areas are foci of lime salt. (Hæmalum and eosin stain: ×200.)

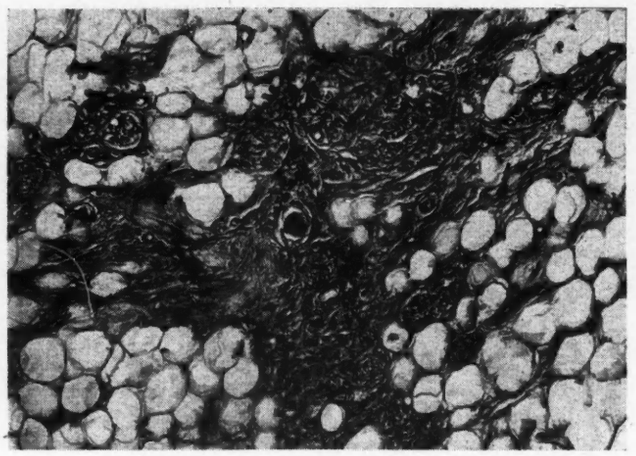


Fig. 4.—Nerve fibres and glial tissue surrounded by adipose tissue. One ganglion cell is present in the centre of the field. (Hæmalum and eosin stain: ×250.)

Histologic observations.—Multiple sections of the tumour from various levels were studied using hæmalum and eosin stain, Bodian stain for nerve fibres, Weil and Pal-Weigert stains for myelin sheaths, Mallory phosphotungstic acid-hæmatoxylin stain, Masson trichrome stain, and the Mallory-Heidenhain aniline blue stain.

The tumour consisted of mature adipose tissue partially surrounded by a thin fibrous capsule. At one level it infiltrated the midbrain and was separated from the ependyma by a very thin zone of glial tissue (Fig. 2). Throughout the adipose tissue were groups of myelinated nerves interpreted as elements of the trochlear nerves. In some areas these were surrounded by hyperplastic Schwann cells which had a whorled arrangement. Foci of brain tissue were incorporated in the tumour and showed irregular deposits of lime salts (Fig. 3). Similar foci of calcification were present in the adjacent brain tissue. Several ganglion cells were identified (Fig. 4). Small arteries and arterioles were present throughout the tumour but did not suggest a hæmangiomatous component. No osteoid tissue or smooth muscle was identified.

The final diagnoses were: lipomatous tumour of the dorsal midbrain with perforation of the adjacent anterior medullary velum; partial obstruction of the aqueduct of Sylvius; hydrocephalus; extreme thinning of the skull; extensive fractures of the skull; lacerations of the cerebral cortex; hæmatoma of the scalp, left side of the face and neck; myocardial hypertrophy; and pulmonary œdema.

DISCUSSION

Lipomas of the central nervous system arise from the pia mater or are at least intimately related to it. This group of lipomatous tumours must be differentiated from lipomatous meningiomas that possess a definite dural attachment and consist of a mixture of adipose and meningiomatous tissue. Any theory of origin of intracranial lipomas must explain the intimate connection with the pia mater, the almost constant location in or near the midline, and the frequently associated neuro-ectodermal abnormalities.

Virchow in 1863, cited by Sperling and Alpers,[2] suggested that cerebral lipomas arose from fat cells that were scattered normally throughout the leptomeninges. Against such a theory is the statement of Wells[9] that adult fat cells do not reproduce themselves. Also, if such were the case, lipomas should not be restricted to a sagittal location. Origin from fibrous or glial tissue is very improbable. Ehni and Love[10] favour an origin from primitive mesenchymal cells in the pia mater. They suggest that lipomatous transformation of these cells is normally held in check by the neuro-ectodermal component of the leptomeninges. When there is a local deficiency or dysraphic defect of neural crest elements, the controlling or inhibiting force is removed and the mesenchymal cells may give rise to lipomatous masses. This theory would explain the fairly constant sagittal location and the often associated developmental neuro-ectodermal abnormalities. The origin from the primitive mesenchyme would account for the finding in some lesions of hæmangiomatous and osteoid elements.[1, 2]

Adair, Pack and Farrior[11] presented evidence which indicated that multiple lipomas and congenital lipomas are related to the peripheral nerves, and they suggested a possible neurogenic origin. The tumour reported by us contained myelinated nerve fibres. They were, however, thought to be the decussated fibres of the trochlear nerves which became surrounded by the growing lipoma. The same interpretation is applied to the presence of glial tissue and ganglion cells. Vonderahe and Niemer[1] made the same observations for their second case, and Crosby, Wagner and Nichols[12] observed the incorporation of spinal nerve fibres in an intraspinal lipoma. This association of lipomas with intracranial and intraspinal nerves raises the question of a neurogenous or nerve sheath origin. Stout[13] stated that Schwann cells seemed able to produce fat. However, until there is more evidence than "guilt by association", intracranial lipomas should be considered to arise from the mesenchyme of the pia mater. The presence of nerve fibres and ganglion cells is the result of incorporation of these structures by growth and infiltration.

The history of this case suggests that the lipoma may have been present from birth or shortly thereafter. There are a few reports in the literature of congenital intracerebral lipomas, but most of these have been multiple and frequently associated with other congenital lesions.[14] These lesions are probably developmental heterotopias or hamartomas. The presence of fibrous, hæmangiomatous and osteoid elements in some of the reported examples of lipomas supports such a concept. The lipoma that is reported here may actually be of a similar nature although there were no other congenital lesions.

Most of the intracranial lipomas reported were symptomless and produced no significant changes in the brain or skull. This lipoma is a relatively large one and by obstruction of the ventricular system in the region of the midbrain caused hydrocephalus with marked thinning of the skull. The severe headaches and the possible increase in size of the head for approximately one year before death may be attributed to increased intracranial pressure and to the internal hydrocephalus. The automobile accident which caused death was a very minor one, but sufficient to produce many fractures in a very thin skull and severe laceration of the cerebral cortex.

SUMMARY

A lipoma of the dorsal midbrain in a 25-year-old male is reported. This is believed to be the ninth recorded case of a lipoma in this location. It obstructed the aqueduct of Sylvius at its junction with the fourth ventricle and caused internal hydrocephalus. The tumour may have been present from birth. Death occurred after a very minor automobile accident and was due to extensive cerebral laceration and multiple fractures in a very thin atrophic skull.

Fasciculi of the trochlear nerves, glial tissue, and several ganglion cells were present in the lipoma. They were not considered a component of the tumour but were thought to have become included by growth and infiltration. Present evidence indicates that this type of tumour develops from the primitive mesenchyme in or close to the pia mater, and that it may be of a hamartomatous nature.

REFERENCES

1. VONDERAHE, A. R. AND NIEMER, W. T.: *J. Neuropath. & Exper. Neurol.*, 3: 344, 1944.
2. SPERLING, S. J. AND ALPERS, B. J.: *J. Nerv. & Ment. Dis.*, 83: 13, 1936.
3. BAILEY, P. AND BUCY, P. C.: *Am. J. Cancer*, 15: 15, 1931.
4. EHNI, G. J. AND ADSON, A. W.: *Arch. Neurol. & Psychiat.*, 53: 299, 1945.
5. EWING, J.: Neoplastic diseases, 4th ed., W. B. Saunders Company, Philadelphia, 1940.
6. LIST, C. F., HOLT, J. F. AND EVERETT, M.: *Am. J. Roentgenol.*, 55: 125, 1946.
7. NORDIN, W. A., TESLUK, H. AND JONES, R. K.: *A.M.A. Arch. Neurol. & Psychiat.*, 74: 300, 1955.
8. BARBER, M. R.: *Canad. M. A. J.*, 63: 495, 1950.
9. WELLS, H. G.: *J. A. M. A.*, 114: 2177, 1940.
10. EHNI, G. AND LOVE, J. G.: *Arch. Neurol. & Psychiat.*, 53: 1, 1945.
11. ADAIR, F. E., PACK, G. T. AND FARRIOR, J. H.: *Am. J. Cancer*, 16: 1104, 1932.
12. CROSBY, R. M. N., WAGNER, J. A. AND NICHOLS, P., JR.: *J. Neurosurg.*, 10: 81, 1953.
13. STOUT, A. P.: Tumors of the peripheral nervous system, Atlas of tumor pathology, Section II, Fascicle 6, Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Armed Forces Institute of Pathology, Washington, D.C., 1949.
14. BAKER, A. B. AND ADAMS, J. M.: *Am. J. Cancer*, 34: 214, 1938.

SYNCOPAL ATTACKS FOLLOWING QUINIDINE ADMINISTRATION

F. GERARD ALLISON, F.R.C.P.[C],
Winnipeg, Man.

A WOMAN of 40 with pure mitral stenosis and auricular fibrillation had a successful commissurotomy in November 1956. She was discharged on digitoxin 0.1 mg. daily and maintained on this dosage. In March 1957, her doctor attempted conversion to normal rhythm with quinidine. Small doses were given without effect except for mild vomiting. On the evening of March 15, a total of 25 grains (1.6 g.) of quinidine was given, the last dose at 10:30 p.m. She vomited all night and had some diarrhœa. In the morning she had three brief episodes of unconsciousness without convulsion.

She was admitted at 11:00 a.m. to St. Boniface Hospital where a further attack of unconsciousness was observed; pulse and blood pressure disappeared but rapid heart sounds could still be heard. Pronestyl (procaine amide) 150 mg. was given intravenously.

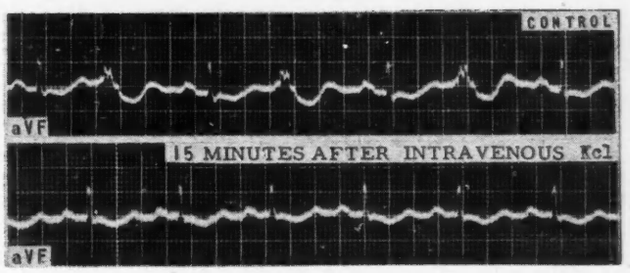


Fig. 1.

When I saw her at 12:30 p.m., she was confused, presumably because of episodes of cerebral anoxia, but not dyspnœic; B.P. 120/80 mm. Hg; E.C.G. showed a normal rhythm of 40, plus an equal number of ventricular extrasystoles (pulsus bigeminus). Comparison with the preoperative E.C.G. showed marked reduction of the right ventricular hypertrophy. There was sagging of ST intervals, due to digitalis or a low potassium level. A striking feature was prolongation of the QT or QU interval to 0.44 second, normal QT being about 0.34 at this rate. Digitalis shortens the QT interval, quinidine prolongs it. Hypopotassæmia occasionally lengthens the QT interval slightly, but frequently gives apparent lengthening, as the U wave is increased in size and may blend with the T wave.[9]

As the last dose of quinidine had been taken 14 hours previously, 70% of the absorbed quinidine should have left the blood, apart from what was lost in vomitus and stool. Studies[1] have shown that eight hours after ingestion of quinidine the blood level is down 50% from its peak, which is attained in two hours. It was concluded that the patient had hypopotassæmia brought on by the quinidine-induced diarrhœa and vomiting, and that this had caused digitalis intoxication which led to episodes of ventricular paroxysmal tachycardia with syncope. Unfortunately the laboratory was closed for the week-end, so that blood levels of potassium could not be determined. The following treatment was instituted: 750 mg. Pronestyl was given orally; chlorpromazine (Largactil) 25 mg. intramuscularly for nausea, and

20 mEq./l. of potassium chloride was given in 500 c.c. saline intravenously. Intake of fruit juice and broth was encouraged because of their potassium content. During the afternoon the patient remained without syncope. She received 250 mg. of Pronestyl orally at 2:30 p.m. and 5:00 p.m.

At 9:00 p.m. another attack of syncope occurred. A direct-writer cardiograph at the bedside showed the tracing to be unchanged. Infusion of another 20 mEq./l. of potassium in saline was started, and a small strip of lead AVF was taken every few minutes. In 15 minutes the extrasystoles disappeared, never to return. Another 20 mEq./l. potassium was given two hours later, followed by oral tablets of potassium chloride. The QT interval and sagging ST interval remained unchanged until the following morning.

There were no further symptoms and the patient was discharged 48 hours later. She remains well, in normal rhythm, and takes no medication.

In recent years it has been recognized[2] that digitalis intoxication can be readily induced in a fully digitalized patient by potassium loss, e.g. after a mercurial diuresis, or by reducing the plasma level of potassium by a high carbohydrate meal, intravenous glucose or insulin. In fact, E.C.G. control after 25 g. of glucose intravenously is a test for borderline digitalis toxicity. Six of seven patients so tested[3] developed extrasystoles within 90 minutes, and one had paroxysmal ventricular tachycardia which was controlled by intravenous potassium.

Administration of potassium and procaine amide has been recognized[4] as the best treatment for digitalis intoxication. Very recently a new method of treating digitalis intoxication with EDTA (ethylenediamine tetra-acetic acid) was introduced.[5] Sodium or magnesium ethylenediamine tetra-acetic acid, a chelating agent given intravenously, lowers blood calcium and rapidly abolishes arrhythmias due to digitalis. There is a synergistic relationship between digitalis and calcium. The chelation treatment should be followed by potassium administration to prevent recurrence of symptoms.

This patient had been on a maintenance dose of digitoxin (Crystodigin, Purodigin, etc.). The incidence of cases of digitalis poisoning increased enormously after introduction of these drugs.[6] Frequently arrhythmias were the first sign of overdosage.[7] Toxicity persists longer than with other digitalis bodies.

When a patient reacts with vomiting or diarrhœa to a small dose of quinidine, it is wise to prevent these symptoms by giving paregoric (camphorated opium tincture) before larger doses are administered.[8] This not only makes administration of therapeutically effective doses possible but prevents unpleasant side effects, and also prevents loss of potassium in vomitus or stool.

REFERENCES

1. DELEVETT, A. F. AND POINDEXTER, C. A.: *Am. Heart J.*, 32: 697, 1946.
2. LOWN, B. *et al.*: *Proc. Soc. Exper. Biol. & Med.*, 76: 797, 1951.
3. PAGE, E.: *Am. J. Med.*, 19: 169, 1955.
4. LOWN, B. AND LEVINE, S. A.: *New England J. Med.*, 250: 866, 1954.
5. GUBNER, R. S. AND KALLMAN, H.: *Am. J. M. Sc.*, 234: 136, 1957.
6. FLAXMAN, N : *Ibia.*, 216: 179, 1948.
7. DEGRAFF, A. C., BATTERMAN, R. C. AND ROSE, O. A.: *J. A. M. A.*, 138: 475, 1948.
8. GOLDMAN, M. J.: *Am. J. M. Sc.*, 222: 382, 1951.
9. SURAWICZ, B. *et al.*: *Circulation*, 16: 750, 1957.

417 Medical Arts Bldg.

SHORT COMMUNICATIONS

TREATMENT OF SUPERFICIAL EPITHELIOMATOSIS WITH AN OINTMENT CONTAINING DEMECOLCIN

ROBERT JACKSON, M.D.,* *Regina, Sask.*

SUPERFICIAL EPITHELIOMATOSIS is a type of basal cell carcinoma. Clinically it usually occurs on the trunk as multiple, superficial, circular, scaly or crusted lesions. Careful examination reveals a fine, pinhead-sized, pearly border. This indurated border can be more easily felt than seen. The tumour grows very slowly and only rarely becomes true invasive basal cell carcinoma. It may be one of the late cutaneous sequelæ to prolonged arsenic ingestion. Confusion with a patch of chronic dermatitis may easily occur. Histologically, there are multiple flask-shaped buds of basal cell carcinoma arising from the overlying epidermis. These buds rarely penetrate deeper than the upper half of the corium, i.e. about 0.6 mm.

Treatment by ordinary radiotherapy or surgical excision is not the treatment of choice, because there will be destruction or removal of much more tissue than is necessary. Also, as the lesions frequently are multiple (up to 100) and large (up to 5 cm. in diameter), extensive areas of radiodermatitis or numerous unsightly scars will result.

Destruction of these tumours by carbon dioxide snow or slush, liquid nitrogen, very superficial radiotherapy or electrodesiccation and curettage has given satisfactory results, with less or none of the aforementioned sequelæ.

Colchicine has long been known to have an inhibiting action on mitoses by blocking cell division during metaphase. It was only natural that it would be tried in neoplastic conditions which have a high rate of mitotic activity. However, colchicine was also found to affect normal tissues. An alkaloid of colchicine, demecolcin, was isolated in 1950 by Santavy and Reichstein[1] and was found

*From the Division of Dermatology, Medical Arts Clinic, Regina, Saskatchewan
Author's present address: 310 O'Connor St., Ottawa.

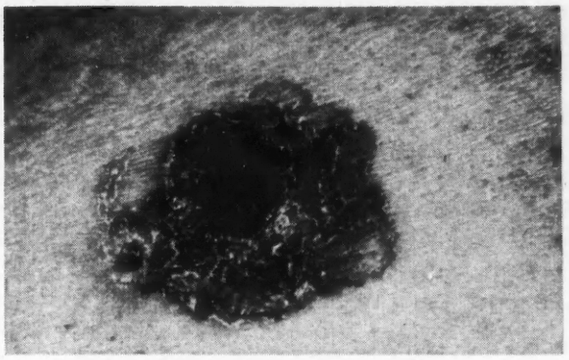


Fig. 1.—Lesion July 24, 1957. (From 35 mm. colour transparency.)

Fig. 2.—Biopsy July 17, 1957. Note at least four "buds" of basal cell carcinoma arising from epidermis. (Hæmatoxylin and eosin × 17.)

to be less toxic to normal tissues. Numerous reports of its action in various skin cancers, including superficial epitheliomatosis, have been published by European and South American authors.[2-4] To my knowledge this is the first report of its use in the United States or Canada.

Mr. L.S., aged 49, a caretaker, was referred to me on July 17, 1957, for a nonhealing sore on his left shoulder. He did not remember when it started, but it was present in 1951 and was biopsied by another doctor. He was told that there was no cancer. I have been unable to trace this biopsy. My examination revealed a solitary typical patch of superficial epitheliomatosis measuring 3.2 by 3.2 cm. on his left shoulder (Fig. 1). Biopsy confirmed the clinical diagnosis (Fig. 2). An ointment containing 0.1% demecolcin* was applied 40 times from July 25 to October 28. By experimenting, I found that daily applications produced the best effect. In fact, if daily applications had been used it seems likely that the number of applications would have been much fewer than 40. The ointment was applied in a thin layer and covered by a Telfa† dressing which was held in place by adhesive tape. With daily applications there was some very superficial ulceration. However, except on direct pressure, this was not painful. The tumour rapidly decreased in size and the small indurated papules became no longer palpable. After the 40th application all the areas were smooth and soft, except for one small indurated area. This was biopsied and showed only an intense inflammation in the upper corium (Fig. 3). Follow-up examination in December 1957 showed no evidence of recurrence (Fig. 4).

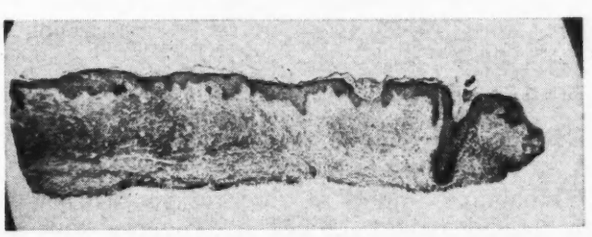


Fig. 3.—Biopsy October 28, 1957. Shows a dense inflammatory infiltrate in upper corium at left of photomicrograph. No evidence of tumour. (Hæmatoxylin and eosin × 17.)

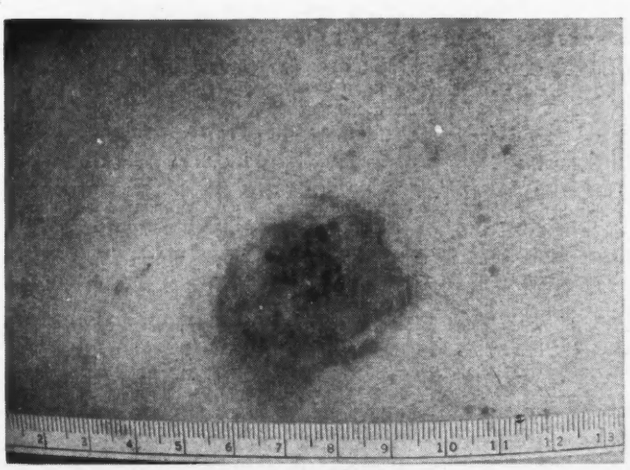


Fig. 4.—Lesion December 5, 1957.

COMMENTS

There is no doubt that demecolcin ointment will destroy the small basal cell carcinomas of superficial epitheliomatosis. Whether this destruction is complete and permanent cannot yet be said. The important fact is that we have a new agent which shows promise in the treatment of superficial epitheliomatosis, and probably in other superficial skin cancers. The cure rate of 50% reported by Fischer[2] is low when compared with cure rates obtained by other methods. Modifications in the type of administration, the strength of demecolcin, or even the demecolcin itself, may be necessary to increase the cure rate. However, because of the simplicity of treatment, these modifications should be investigated.

SUMMARY

A case of superficial epitheliomatosis was treated and apparently cured (at least for two months) by 40 applications of an ointment containing 0.1% demecolcin.

I am indebted to Mr. H. Wood for the photographs and photomicrographs.

REFERENCES

1. SANTAVY, F. AND REICHSTEIN, T.: *Helvet. chim. acta*, 33: 1606, 1950.
2. FISCHER, E.: *Dermatologica*, 112: 426, 1956.
3. TELLO, E. AND FERRARIS, L. V.: *Ibid.*, 112: 230, 1956.
4. COTTINI, G. B. AND RANDAZZO, S. D.: *Ibid.*, 110: 426, 1955.

*Supplied by Ciba Company Limited, Montreal, under the trade name of Colcemide.

†Made by Kendall Company, Chicago, Illinois, U.S.A.

Canad. M. A. J.
June 15, 1958, vol. 78

FURTHER FIGURES ON LOST TIME DUE TO SICKNESS AND ACCIDENT IN INDUSTRY*

A. H. SELLERS, B.A., M.D., D.P.H.† and
R. B. SUTHERLAND, M.D., D.P.H.,‡
Toronto

THIS REPORT presents a summary of some data on absences due to sickness and accident among employees of eight companies during 1956. A similar report, previously published,[1] presented data on the combined experience of eight companies for the year 1954; six of the companies included in the previous report are also included in the present one.

For the recording of lost-time morbidity each company used either the marginal punch card or the dual-purpose card system designed by the Divisions of Industrial Hygiene and Medical Statistics. The records on which this report is based were prepared by the medical departments of the companies and made available to the Ontario Department of Health for analysis.

SCOPE AND METHOD

The medical department of each of the companies maintained a record of all absences due to sickness or accident lasting one calendar day or longer. Both of the systems used make provision for the recording of the following essential information: name, sex, age, department, occupation, order of absence, date absence began, date absence ended, calendar days lost, diagnosis, whether occupational or non-occupational, and the termination of the absence. The marginal punch card system also provided for identification of the number of times the employee was absent.

The summary of the morbidity experience included here is that of the combined staffs of the eight companies. The average population comprised 5889 persons, 3758 males (64%) and 2131 females (36%). The data cover all absences due to sickness or accident which began during 1956, and which caused loss from work of one full calendar day or more.

Diagnoses were tabulated according to seven *condensed diagnosis groups*. The inclusions within these seven condensed diagnosis groups correspond with groupings used in the International Statistical Classification of Diseases, Injuries and Causes of Death, W.H.O., 1948.

The following three indices of morbidity were computed:

I. Frequency rate—Annual number of absences per 100 persons.

II. Disability rate—Annual number of days lost per person.

III. Severity rate—Average number of days lost per absence.

These indices were computed for each sex by age group and by *condensed diagnosis group*. The number of persons used in the calculations of indices I and II was the mean of the total numbers of persons on the payroll of each of the eight companies at three intervals during the year, distributed by sex and age group (Table I).

TABLE I—AVERAGE NUMBER OF PERSONS EMPLOYED BY AGE GROUP AND SEX

Age group	*Males*	*Females*	*Both Sexes*
Under 25	501	840	1,341
25 - 34	1,293	713	2,006
35 - 44	1,109	319	1,428
45 - 54	584	172	756
55 and over	271	87	358
Total	3,758	2,131	5,889

STATISTICAL ANALYSIS

There were 3369 persons absent during the year (1619 males and 1750 females). The total male employees absent amounted to 43% of the average number of males employed; female employees absent amounted to 82% of the average number of females employed.

Of the 7529 absences due to sickness or accident during the year, 2793 (37%) were male absences and 4736 (63%) were female absences. These absences were responsible for the loss of 40,354 calendar days. Of the total number of days lost, 20,571 (51%) were accounted for by male personnel and 19,783 (49%) by female personnel.

MORBIDITY EXPERIENCE BY AGE

The three morbidity indices, by age group and sex, are presented in Table II.

The annual number of absences per 100 persons was 74 for males and 222 for females. The frequency rate was highest at ages under 25 years for both males and females. The annual number of calendar days lost per person among males was 5.5 days and among females 9.3 days. The highest disability rate for both sexes occurred in the age group 55 years and over. The average number of days lost per absence for all males was 7.4 days and among all females 4.2 days. The severity rate was highest for each sex at ages 55 years and over.

The number of absences per 100 persons at all ages was greater for females than for males, the M:F ratio being 1:3.0. The number of days lost per person was greater for females than for males, the M:F ratio being 1:1.7. The average number of days lost per absence was greater among males than among females, the M:F ratio being 1:0.6. When menstrual disorders and complications of pregnancy are excluded, the frequency and dis-

*Prepared by the Division of Industrial Hygiene and the Division of Medical Statistics, Ontario Department of Health, Toronto, March 1958.

†Director, Division of Medical Statistics.

‡Division of Industrial Hygiene.

TABLE II.—MORBIDITY INDICES BY AGE GROUP AND SEX

Age Group	I. Frequency rate: Annual number of absences per 100 persons		II. Disability rate: Annual number of days lost per person		III. Severity rate: Average number of days lost per absence	
	Male	Female	Male	Female	Male	Female
Under 25	108	280	5.6	9.1	5.1	3.3
25 - 34	64	217	3.4	10.0	5.3	4.6
35 - 44	67	176	5.2	9.2	7.8	5.2
45 - 54	76	106	8.4	7.0	11.0	6.6
55 and over	83	105	10.0	10.3	12.1	9.8
Total	74	222	5.5	9.3	7.4	4.2

ability ratios decrease to 1:2.7 and 1:1.5 respectively, while the ratio of the severity rates remains unchanged.

DURATION OF ABSENCES

The relative importance of absences of various durations in the total picture is demonstrated by Table III.

TABLE III.—PERCENTAGE DISTRIBUTION OF DURATION OF ABSENCES IN CALENDAR DAYS, BY SEX

Duration in calendar days	Absences		Calendar days	
	Male	Female	Male	Female
1	40.0	50.0	5.4	12.0
2	11.6	11.3	3.2	5.4
3	11.8	13.2	4.8	9.5
4 - 7	18.0	16.8	13.3	20.6
8 - 28	12.6	6.5	25.1	22.5
29 - 91	5.0	1.9	31.2	22.8
92 and over	1.0	0.3	17.0	7.2
Total number	2,793	4,736	20,571	19,783

Absences lasting one calendar day accounted for the bulk of the total absences—40.0% of male absences and 50.0% of female absences. Absences of three calendar days or less accounted for 63.4% of male absences and for 74.5% of female absences, but for only 13.4% of the calendar days lost by males and for 26.9% of the calendar days lost by females.

Of the total number of absences among males, 18.6% lasted eight calendar days or longer and these absences contributed 73.3% of the total number of days lost. Among females, 8.7% of all absences lasted eight calendar days or longer and contributed 52.5% of the total number of days lost.

PRINCIPAL CAUSES OF ABSENCE

The three morbidity indices by sex and condensed diagnosis groups are set out in Table IV.

For acute upper respiratory infections,* the frequency rate was more than three and one-half times as high for females as for males, while the severity rate was one-half day less for females than for males.

Male personnel lost an average of 0.7 calendar day during the year because of the acute upper respiratory diseases, compared with 2.0 days among females. Males also lost fewer days because of diseases of the digestive system (1.0 to 1.7).

For "other specified causes", the females experienced about twice as many absences as did the males, but each of their absences was about four and one-half days shorter.

The number of days lost per person because of accidents was low for both males and females (one day for males, one-half day for females). Male personnel lost about five and one-half days more per accident than did female personnel.

*Includes: common cold, coryza, acute sinusitis, acute tonsillitis.

TABLE IV.—MORBIDITY INDICES BY CONDENSED DIAGNOSIS GROUP AND SEX

Condensed diagnosis group	I. Frequency rate: Annual number of absences per 100 persons		II. Disability rate: Annual number of days lost per person		III. Severity rate: Average number of days lost per absence	
	Male	Female	Male	Female	Male	Female
Acute upper respiratory infections	21	74	0.7	2.0	3.1	2.6
Other diseases of the respiratory system	15	24	0.7	1.0	4.6	4.2
Diseases of digestive system	15	48	1.0	1.7	6.6	3.5
Disorders of menstruation	—	21	—	0.5	—	2.3
Symptoms and ill-defined conditions	5	25	0.1	0.6	2.5	2.4
Accidents and violence	6	5	1.0	0.5	16.6	11.0
Other specified causes	12	25	2.0	3.0	16.3	11.9
Total	74	222	5.5	9.3	7.4	4.2

MORBIDITY BY CLASS-DIVISION

Occupational conditions accounted for only 4.1% of the absences and 11.7% of the days lost among males, and for only 0.5 and 2.2% among females.

Accidents contributed 8.2% of the absences and 18.5% of the days lost for males, compared with 2.3% and 6.1% for females.

REFERENCE

1. SELLERS, A. H. AND SUTHERLAND, R. B.: *Canad. M. A. J.*, 75: 418, 1956.

VITAMIN B_6 IN MENTAL DEFICIENCY: XANTHURENIC ACID EXCRETION IN PHENYLKETONURICS*

B. TISCHLER, M.D. and
E. G. McGEER, Ph.D., *Vancouver, B.C.*

PHENYLKETONURIA is one of the conditions in which mental deficiency is associated with a demonstrable metabolic disorder. It is fairly well established that in phenylketonurics there is a defect in the enzymic system for the hydroxylation of phenylalanine. Phenylalanine accumulates in the blood and is excreted in the urine together with its derivatives, phenylpyruvic acid, phenyllactic acid and phenylacetyl-glutamine. No correlation has been found between the amount of phenylpyruvic acid excreted and the level of intelligence.[3] There is a possibility that the transamination of phenylalanine to phenylpyruvic acid is a detoxication reaction, especially if one considers that most authors[4, 6, 7] have not detected significant amounts of phenylpyruvic acid in the blood. Jervis[10] found 0.31-1.78 mg. % of phenylpyruvic acid in plasma, but his analytical method is not believed to be specific.

Studies on animals indicate that vitamin B_6 plays an important role in transamination reactions.[13] In phenylketonurics there is probably a constant demand for this vitamin in the transamination of phenylalanine to phenylpyruvic acid, and it was felt that it would be of interest to investigate the possibility of vitamin B_6 deficiency in phenylketonurics. A vitamin B_6 deficiency would be consistent with the finding of low serum levels of 5-hydroxytryptamine in phenylketonurics[12] since vitamin B_6 is known to be a coenzyme required for the synthesis of this tryptophan metabolite.[17]

Until recently it was thought that vitamin B_6 deficiency did not occur in man. Now it is known to be associated with convulsions[1] and may occur even with a normal intake in certain predisposed infants. Vilter *et al.*[15] used desoxypyridoxine (a specific antagonist of the B_6 group) to induce vitamin B_6 deficiency in humans. The clinical signs and symptoms are reported to be anorexia, nausea, listlessness and lethargy, dermatitis resembling seborrhœa sicca, polyneuritis and lymphocytopenia.[14]

Convulsions and skin changes are frequently observed in phenylketonuria. Of the 21 cases in our residential school, four had eczema in infancy or early childhood but it is not present now. Another four patients show signs of dermatitis at present; two of them are on a diet low in phenylalanine and have shown considerable improvement of the skin lesions, as will be reported in a separate communication. Eight of the 21 cases have a history of convulsions and a few are still not seizure-free.

Bickel *et al.*[2] tested the effect of feeding vitamin B_6 to phenylketonurics. The vitamin was given for 7 to 14 days and no noticeable changes were observed, either in the plasma levels of phenylalanine and tyrosine or in the urinary excretion of phenylalanine and phenylpyruvic acid.

The usual biochemical test for vitamin B_6 deficiency is an indirect one. It is known that vitamin B_6 is essential for normal tryptophan metabolism. When tryptophan metabolism is deranged because of B_6 deficiency, an abnormal metabolite, xanthurenic acid, is excreted in the urine.[11, 15] Usually xanthurenic acid increases in urine long before the symptoms and signs of vitamin B_6 deficiency are manifested clinically.[15] Excessive amounts of tryptophan in the diet accentuate xanthurenic acid excretion in vitamin B_6 deficiency.[15] Such excretion has been used to demonstrate subclinical vitamin B_6 deficiencies, particularly in pregnant women.[5, 9, 16]

MATERIAL AND METHODS

Seven patients with phenylketonuria were selected for this study. We chose the more cooperative patients because 24-hour urine collections seemed desirable for the estimation of xanthurenic acid. Their ages ranged from 10 to 43 years and their intelligence from the idiot to the moron level. Six patients were taken as controls; five were diagnosed as cases of simple amentia and one as a mongolian idiot. All had been living in the hospital environment and eating the standard hospital diet for some time.

Xanthurenic acid was estimated by the method of Glazer[8] on 24-hour urine specimens before and after a 10-gram load of DL-tryptophan.[8, 15] Preliminary experiments indicated that phenylpyruvic acid in urine did not interfere with the xanthurenic

*From The Woodlands School, New Westminster (residential school for retarded children), and the Department of Neurological Research, University of British Columbia.

acid analysis and that recovery of added xanthurenic acid was 100-96% at the 20-50 mg./1000 c.c. level. Duplicate analyses on the same urine specimens checked within 98/100%.

Repeated analyses on separate 24-hour urine specimens from the same individual indicated that there was considerable day-to-day variation in xanthurenic acid excretion: one patient excreted 6 mg. on one day and 12 mg. on a second day; a second patient excreted 5 mg. on one day and 8 mg. on a second day.

TABLE I.—XANTHURENIC ACID EXCRETION IN 7 PHENYLKETONURICS AND IN 6 CONTROLS BEFORE AND AFTER A TRYPTOPHAN LOAD

Name	*Age*	*Intelligence*	*Xanthurenic acid in mg./24 hours*	*Xanthurenic acid after tryptophan load, mg./24 hrs.*
A. *Phenylketonurics*				
H.R.	43 years	Moron	6	11
B.T.	37 "	Moron	13	14
S.D.	18 "	Imbecile	5	5
M.D.	18 "	Imbecile	9	5
E.A.	17 "	Idiot	9	10
S.J.	14 "	Idiot	20	22
A.L.	10 "	Imbecile	6	7
Average for phenylketonurics.....			9.7	10.6
B. *Controls*				
J.E.	21 years	Imbecile	5.6	11.5
H.H.	20 "	Moron	7	10
B.E.	19 "	Moron	15	20
K.P.	17 "	Moron	8	7
F.M.	14 "	Moron	7	8
W.S.	10 "	Imbecile	6	6
Average for controls.....			8.6	10.4

It is evident from the data in Table I there is no significant difference between the phenylketonuric and the control group in xanthurenic acid excretion either on a normal diet or after a tryptophan load.

Two normal adult women, not on the hospital diet, were found by us to excrete 2 and 3 mg. a day, respectively. Normal values for xanthurenic acid excretion are reported in the literature to be 0-30 mg. a day,[15] the xanthurenic acid being determined by the same method as used here. It appears therefore that the excretion by all the phenylketonurics and controls was within normal limits.

DISCUSSION AND SUMMARY

The data reported here indicate that xanthurenic acid excretion in a group of phenylketonurics does not differ significantly from that in another group of mental defectives. In both groups the values found were within normal limits. It therefore appears unlikely that phenylketonurics on an adequate diet will be deficient in vitamin B_6, and the study suggests that vitamin B_6 supplementation experiments would only be useful for the purpose of investigating the effect of B_6 excesses in phenylketonuria.

The authors wish to express their gratitude to the Superintendent of the Woodlands School, Dr. L. A. Kerwood, for his assistance and encouragement; to Dr. Henry G. Dunn, Assistant Professor of Pædiatrics, for his suggestions and comments; and to Mrs. A. Vallis, B.A., for her technical assistance in carrying out the estimations of xanthurenic acid.

REFERENCES

1. BESSEY, O. A., ADAM, D. J. AND HANSEN, A. E.: *Pediatrics*, 20: 33, 1957.
2. BICKEL, H. *et al.*: Biochemistry of the Developing Nervous System, edited by Walsh, 1955.
3. JERVIS, G. A.: *Proc. Soc. Exper. Biol. & Med.*, 75: 83, 1950.
4. BOREK, E. *et al.*: *Ibid.*, 75: 86, 1950.
5. CHIANCONE, F. M. *et al.*: *Arch. Biochem.*, 54: 15, 1955.
6. CLOSS, K. AND FÖLLING, A.: *Ztschr. physiol. Chem.*, 254: 250, 19 8.
7. EDSON, N. L.: *Biochem. J.*, 29: 2498, 1935.
8. GLAZER, H. S. *et al.*: *Arch. Biochem.*, 33: 243, 1951.
9. GLAZER, H. S. *et al.*: *Ibid.*, 42: 98, 1953.
10. JERVIS, G. A.: *Proc. Soc. Exper. Biol. & Med.*, 81: 715, 1952.
11. LEPKOVSKY, S., ROBOL, E. AND HAAGEN-SMITH, A. J.: *J. Biol. Chem.*, 149: 195, 1943.
12. PARE, C. M. B., SANDLER, M. AND STACEY, R. S.: *Lancet*, 1: 551, 1957
13. SCHLENK, F. AND SNELL, E. E.: *J. Biol. Chem.*, 157: 425, 1945.
14. SPIES, T. D., BEAN, W. B. AND ASHE, W. F.: *J. A. M. A.*, 112: 2414, 193[illegible].
15. VILTER, R. W. *et al.*: *J. Lab. & Clin. Med.*, 42: 335, 1953.
16. WACHSTEIN, M. AND GUDAITIS, A.: *Ibid.*, 40: 550, 1952.
17. WEISSBACH, H. *et al.*: *J. Biol. Chem.*, 227: 617, 1957.

CARCINOMA OF THE COLON AND RECTUM

In an analysis of 1023 patients with carcinoma of the colon or rectum seen during the 25-year period ending December 1955, Postlethwait *et al.* (*Surg. Gynec. & Obst.*, 106: 275, 1958) have produced some interesting tables and bar graphs to illustrate the various clinical and pathological features. About 75% occurred in the rectal and sigmoid segments. The relative frequency of major symptoms in the right and left colon and rectum is comparable with that in other studies. The classical triad of abdominal pain, change in bowel habit and change in stool was again obvious. Of the rectal lesions 94% were palpable by rectal examination and the remainder were seen by proctoscopy.

The procedure of choice for rectal and rectosigmoidal lesions was the one-stage combined abdominoperineal resection of Miles with only infrequent use of sphincter-preserving pull through procedures. A tendency was noted to use anterior resections more often in recent years for the high rectal lesion. The reverse is true for low rectal lesion because of the tendency of lateral spread. There has been a tendency to do more anterior resections on the midrectal lesion (6 to 15 cm.).

Referring to Bacon's series, in which multiple polyps were present in 33% of patients, the authors stress the importance of inspecting the bowel with a sigmoidoscope through separate colotomies. It is stated that the risk of developing large bowel cancer is "probably about 5% after having ulcerative colitis for five years, with each year increasing the chances of developing a cancer". The fact that weight loss was present in only a third of these patients once more demonstrates that this complaint should not be necessary to arouse suspicion of malignancy.

At the authors' hospital, neomycin is currently the drug of choice. Proper preoperative preparation and keeping bowel empty after operation were considered of paramount importance. Palliative resection should be employed if possible, for in properly selected patients it does not increase the mortality or morbidity. There has, of course, been greater tendency towards this in recent years because of reduction in loss of blood and relief of obstruction. Removal of the source of sepsis no doubt helps to slow down inanition. These reasons and the statistical evidence of prolongation of life make the policy well worth while.

For the entire group, operability rate was 77% and resectability rate 50%. Mortality rate in the last five years was 3.4% for definitive resections. The five-year survival after resection was 49.5% for rectal, 50.0% for left colon, and 53.7% for right colon cases.

Canad. M. A. J.
June 15, 1958, vol. 78

The Canadian Medical Association Journal

published twice a month by
THE CANADIAN MEDICAL ASSOCIATION
Editor: S. S. B. GILDER, T.D., M.B., B.Sc.
Managing Editor: T. C. ROUTLEY, M.D., F.R.C.P.[C.]
Assistant Editor: M. R. DUFRESNE, M.D.
Editorial Offices: 150 ST. GEORGE ST., TORONTO
(Information regarding contributions and advertising will be found on the second page following the reading material.)

THE CHANGING STATUS OF THE PATIENT

Historians can show that the wealthy and the important do not always receive the best of medical and surgical treatment. The case of the Prince Consort dying of typhoid fever with an incorrect diagnosis comes to mind, as does the extraordinary muddle surrounding the death of the German Emperor Frederick III from laryngeal cancer. Indeed there must be circumstances in which the indigent patient in a teaching hospital bed is in less peril than the socialite with a retinue of capriciously chosen but fashionable attendants.

Throughout the centuries it has been traditional to use only the indigent as teaching material for medical students at all stages, and to safeguard the rich from their contact. Since there is nothing like having a number of keenwitted students watching his every step to keep a physician on his toes, this segregation has not been always to the advantage of the wealthy. But the indigent without provision for sickness are getting less each year, even in a North American society without welfare state concepts. The amount of teaching material available has diminished to the extent that some medical schools now find themselves seriously handicapped. Fear that the new system of hospital insurance in Canada may make further inroads into the supply prompted the Canadian Association of Medical Colleges to present a brief to the Minister of National Health and Welfare last fall, urging that their needs as teachers be taken into account in framing legislation.[1] Similar fears led to a symposium at the 54th Annual Congress on Medical Education and Licensure, held in Chicago last February, on the subject of education and the changing status of patients.[2]

The solution of this problem is both obvious and complex, as the participants in the symposium showed. Clearly, private patients must now be used as teaching material whenever they enter a teaching hospital of any sort. This is the only way to resolve the paradox of an increasing number of hospital beds and a faster turnover of patients on the one hand, and a diminishing pool of teaching cases on the other. Hilliard[3] of Saskatoon gave an excellent example of such a system at work in his description of the operation of the University Hospital in that city. Indeed, the constant whittling down of public ward patients by growth of prepayment schemes, workmen's compensation schemes, veterans' schemes, and so on, renders this step imperative.

The change should be of benefit both to the patient and to the student, for teaching on an indigent population has always given the student an unbalanced view of the pattern of sickness in the community as a whole. He needs to see all sorts and conditions of men to equip himself for practice, and he needs to see them both in and out of hospital.

The problem of the undergraduate student is not a particularly difficult one, for the majority have no objection to co-operating with the student, whatever their status, provided of course that he has been properly instructed in the etiquette of handling patients as human beings without discourtesy and without either fatiguing them or hurting them unnecessarily. But when we come to the graduate or postgraduate level, complications set in. The intern has reached the stage of rendering some services, and this alters his relationship to the patient. When we consider resident training, this factor plays an even more important part.

Contributors to the symposium stressed the need for using community hospitals in graduate and postgraduate training. In the first place, the shift in population means that in many urban areas of North America a significant section of the population has moved out into the periphery of cities and now receives its hospital care in non-teaching hospitals; moreover, the standard of these peripheral hospitals is constantly rising. These hositals have an ample supply of young women with gynæcological or obstetric problems, and also of children. Burgess and Leonard[4] note the efforts made in New England to draw peripheral hospitals into the intern training program. Supervision and the preceptor type of teaching may not be so abundant, but the intern gains in responsibility. Nevertheless, as Hamilton[5] points out, use of peripheral hospitals does mean that the student has for his instructors men who have not indicated any desire to teach, and are successful practitioners rather than teachers.

The changing status of the patient presents its most obvious difficulties when the training of residents is considered, particularly in those specialties with a more personal type of service, such as surgery, gynæcology and obstetrics. Here the question is how to give the resident the gradual increase in responsibility he needs without running into trouble with the patient, the legislator, the tax collector, the insurance agency, and last but not least the local medical society. Lawson[6] suggests a number of devices to help resident training.

He may be given care of the families of students and other staff. He may be given a preceptor, although some would argue that medicine has grown out of the empirical approach associated with preceptorship, with its tendency to reproduce a carbon copy of the instructor. The resident may be farmed out to smaller hospitals for a portion of his training, to give him more responsibility. Lastly, he may be put on the staff of a clinic of private type; this is said to be happening already in the U.S.A. (Zintel[7]), but has a number of drawbacks. It may raise taxation problems, and it may be regarded as unfair competition by the local medical society. Insurance agencies may also have something to say about this practice.

Barnes[8] suggests that there is a need for education of various groups. Established but non-teaching physicians and their societies must be educated into co-operating with rather than opposing educational advances; the duty of educating their successors properly must be regarded as a task which concerns them all. Insurance agencies must be educated into realizing the need for giving the resident patients of his own; if he does not get them during the last stages of his surgical training there is a danger that he may become what Barnes calls "an accomplished technician ghosted to technical aptitude". Lastly, the legislator must be educated into realizing the need for safeguarding the supply of teaching patients when new hospital insurance legislation is being framed. The U.S. symposium closes on a note of warning by Zintel that if we cannot agree on a clear road for the future training of residents, the decisions will be made by other interested groups or by other forces.

REFERENCES

1. Canadian Association of Medical Colleges: *Canad. M. A. J.*, 78: 764, 1958.
2. DARLEY, W. *et al.*: *J. A. M. A.*, 167: 182-214, 1958.
3. HILLIARD, I. M.: *Canad. M. A. J.*, 78: 474, 1958.
4. BURGESS, A. M. AND LEONARD, J. C.: *J. A. M. A.*, 167: 206, 1958.
5. HAMILTON, T. S.: *Ibid.*, 167: 187, 1958.
6. LAWSON, R. B.: *Ibid.*, 167: 200, 1958.
7. ZINTEL, H. A.: *Ibid.*, 167: 211, 1958.
8. BARNES, A. C.: *Ibid.*, 167: 202, 1958.

Editorial Comments

MANAGEMENT OF THE HOPELESS CASE—A CHALLENGE

In a paper on the care of the patient with advanced cancer, Homburger[1] summarizes the management as follows: "The patient with advanced cancer has a right to expect the best of care, the physician's full attention, and any palliative measures that may seem helpful. Much pain can be controlled, nausea can be suppressed, discouragement overcome, some tumours can be slowed, life can be occasionally prolonged and nearly always made tolerable." Recently the Royal Society of Medicine of London held a debate on the management of the hopeless case, at which Gibson[2] spoke of "total" care, including attention to physical, psychological, vocational and special aspects. Both he and the succeeding speaker, Gavey,[3] made a very wide approach to the problem. They felt that the patient's environment had to be adjusted, the relations and friends properly instructed, and the patient inspired with an aggressive attitude to his illness. They emphasized that full advantage should be taken of social and welfare services and of nursing services, now obtainable in the United Kingdom without burdening the patient with extra expense. The patient should be kept fully occupied, gainfully if possible, so as to retain his feeling of being useful to his family and community. No difficulty need be experienced in maintaining a hopeful attitude even in the most obviously incurable case. Have we not seen several incurable diseases become amenable to treatment in the last few decades? Gibson speaks of spiritual therapy as being included automatically in his care of the hopeless case. There can be no doubt about the value of the help which the patient can receive from his clergyman, provided of course that he is prepared to accept it. One may question the wisdom of labelling it "spiritual therapy", as Gibson does, thus reducing it to the level of yet another adjunct to medical treatment. It is as if the family doctor, having tried all the other specialists and found them wanting, is now calling in the clergyman, or should we say spiritual therapist?

A panel discussion was held recently under the auspices of the Section of General Practice of the Academy of Medicine, Toronto, and the North Toronto Medical Society on the topic of religion and medicine. Here minister, rabbi and priest discussed freely their role in the care of the ill as they see it. It soon became obvious that all three speakers considered co-operation with the nursing and medical professions desirable and necessary, and that they were continuously re-examining their relationship with medicine so as to improve this relationship, and yet conform with their religious teachings and principles. Can the same be said from the physician's standpoint? Some of the explanations given at this meeting must have been news to some of the audience; hearing such authoritative explanations must surely prove helpful in the management of patients. This goes particularly for the hopeless cases. What was made quite clear is that clergymen operate on a different level from ours. Our preoccupation is with matters physical and mental, theirs with matters spiritual. Usually these two spheres do not conflict, but when they do the clergyman insists that the spiritual needs take precedence, even if this should cause physical or mental suffering. Whatever we may feel or think of this fundamental difference in approach, we should know about it and try to understand it. To our patients who are seeking help from their spiritual adviser it is important to know that we are not hostile or jealous, and that on the contrary we welcome this help. Panels such as the North Toronto one should be held more often.

Canad. M. A. J.
June 15, 1958, vol. 78

As Gavey points out, the problems of the hopeless case have been attracting increasing interest in recent years. He quotes the titles of such recent publications as "Palliation in Cancer" and "Should the Patient Know the Truth?", and the various writings by laymen themselves victims of incurable diseases, as evidence of this growing interest.

The task of the doctor is difficult, and maintaining interest in the case which has become a "mere" nursing problem may require a special effort on his part. Gibson expresses envy of the doctors of ancient Babylon, who were forbidden by law to care for the hopeless case. One can understand this attitude; yet would this not deprive the doctor of one of his most rewarding spiritual experiences? In this age of scientific medicine the care of the hopeless case offers the doctor one of the few remaining opportunities to practise the art of medicine to its fullest. Drawing on all available resources that medical and social sciences can give him, the doctor can integrate them for the good of the central figure, the patient, and by using ingenuity, intuition and sympathy, help create conditions which will make the patient's life not only tolerable but worth while. The experienced and mature doctor will not follow any set rules on whether or not to tell the patient the whole truth, but even he will sometimes be surprised by the fortitude displayed by his patient.

Yes, care of the hopeless case is a challenge, but it can also be an opportunity to enrich our lives and thus repay us amply for our labours.

W. GROBIN

REFERENCES

1. HOMBURGER, F.: *Geriatrics*, 11: 372, 1956.
2. GIBSON, R.: *Proc. Roy. Soc. Med.*, 51: 111, 1958.
3. GAVEY, C. J.: *Ibid.*, 51: 116, 1958.

INFLUENZA 1957

Although the "Asian" influenza assumed the character of a pandemic during 1957, it is generally agreed that it was mild in nature. It afforded a unique opportunity to isolate the virus and prepare a vaccine before the disease reached the western world. Even so, final preparations for the trials of the vaccine had to be speeded up in Britain, the epidemic having arrived there at least one month earlier than expected. The *British Medical Journal* for February 22, 1958, gives several accounts of British experience. Serologic studies with the vaccine made from the Asian strain A were carried out in Army and Air Force volunteers in Britain, and it was found that the first dose produced only a low antibody titre but the second dose administered three to four weeks later evoked a much greater antibody response. A very definite preventive effect was observed from the vaccine in trials involving altogether some 3000 persons. Comparison with polyvalent vaccine A and vaccine B suggested that these two vaccines gave no protection, whereas the Asian strain vaccine gave a 65% protection rate. The protection became evident nine days after inoculation and lasted throughout the period of observation.[1]

A few cases of influenza bronchopneumonia in children[2] and lobar pneumonia in adults, with sudden death within one to two days of onset in previously healthy persons, have been reported in Britain.[3] It is remarkable how little was found on physical examination of these patients even a few hours before death, yet at autopsy the lungs were massively involved and there was marked engorgement with occasional hæmorrhage of other organs, particularly the stomach.

Another interesting paper in the same issue of the *British Medical Journal* records that although some 34% of the population of Abadan (Iran) were affected the incidence of complications was low and the case fatality rate one in 9000. On the other hand, there has been a marked increase in visits to outpatient clinics since the epidemic, and the author takes this to indicate a rise in the ill-health of the population after the epidemic. The discovery of some new cases of active tuberculosis is also attributed to the after-effects of influenza.[4]

In England and Wales the epidemic attacked a large segment of the population, but the fatality rate was low and even the death rate from diseases which usually accompany influenza was not exceptionally high.[5]

While it is good to know that a vaccine developed for this type of influenza has good protective value, it may not become possible to anticipate the next epidemic because of rapidity of spread. The mystery of the rise and fall of epidemics and their changing virulence is apparently as far from being solved as ever, and we may not be so fortunate in predicting some future major epidemic due to an influenza virus to which we have not been previously exposed. Even now, we cannot be absolutely certain that there will be no more serious sequelæ from the present epidemic. From Vienna comes an isolated report of a noticeable increase in encephalitis since the late summer of 1957.[6] To those of us who still remember the encephalitis following the 1918 influenza this may sound ominous. As the editorial in the *British Medical Journal* puts it, "The world-wide epidemic which we have just witnessed may yet do some good if it stimulates more research into the problem of how to protect a large population quickly against a virulent influenza epidemic."[7]

REFERENCES

1. Medical Research Council, Committee on Influenza and Other Respiratory Virus Vaccines: *Brit. M. J.*, 1: 415, 1958.
2. NEILSON, D. B.: *Ibid.*, 1: 420, 1958.
3. MORGAN, D. M. AND PICKUP, J. D.: *Ibid.*, 1: 263, 1958.
4. ROWLAND, H. A. K.: *Ibid.*, 1: 422, 1958.
5. MARTIN, W. J.: *Ibid.*, 1: 419, 1958.
6. GERSTENBRAND, F., HOFF, H. AND WEINGARTEN, K.: *Wien. med. Wchnschr.*, 108: 1, 1958.
7. Editorial: *Brit. M. J.*, 1: 447, 1958.

TENSION PAIN IN GYNÆCOLOGICAL PRACTICE

A British gynæcologist and a psychiatrist have carried out a joint study of the incidence and nature of pain in a gynæcological clinic.[1] They interviewed 64 cases selected at random from the outpatient department of University College Hospital, London, and observed them for periods up

to 13 months. The age range of the patients was 16-57, with a mean of 33. Out of the total of 64 patients, 22 gave pain as the presenting symptom, and this was much the commonest complaint, for another 12 patients also described pain as one of their complaints.

The most common site of pain was the abdomen, with the back, head and shoulders next in order. The complaint of pain as described by the patient was seldom fully accounted for by physical disorder in the gynæcological field, and an attempt was made to appraise the relative importance of emotional and physical factors in the 22 cases in which pain was the leading symptom. In one case in this group the pain appeared to be entirely of physical origin, and in another five patients it was mainly of physical origin; in nine cases it was mainly of emotional origin with minor physical factors and in seven cases it was predominantly of emotional origin.

The author discusses the distinguishing marks of emotional or tension pain. It is usually symmetrical about the body axis, involves more than one area of the body and is not consistent with the pain distribution of organic disease. It is often continuous from morning to night without relief, in contrast to organic pain, and variations in the intensity of the pain are usually quite plainly related to stress. The pain may be described by the patient as "aching", "dull" or "sharp" or even "burning". In its natural history, tension pain conforms with the criteria of a stress disorder, beginning at a moment of crisis and recurring in attacks related to incidents of stress, only to clear when the stress is removed or the patient learns to adapt to it. In the present series, the distribution of pain differed from that in patients attending a department of physical medicine in that it was commoner in the abdomen and lower part of the body; this would be expected, since the women had been referred to a gynæcological clinic.

The author frankly admits that treatment of tension pain is less rewarding than that of any other category of stress disorder. The majority of patients remained unimproved, despite the best endeavours of the physician, psychiatrist and physiotherapist. The most valuable therapeutic methods are techniques of relaxation, and exploration of the patient's emotional state to discover and deal with sources of anxiety, friction and discontent.

REFERENCE

1. O'NEILL, D.: *J. Obst. & Gynæc. Brit. Emp.*, 65: 106, 1958.

TOBACCO AND PEPTIC ULCERS

With so much information accumulating about the effects of smoking on health in general and on certain organs in particular, it was only natural that some investigators would attempt to establish definitely what effect, if any, tobacco has on the production and maintenance of peptic ulcers.

Doll, Avery Jones and Pygott[1] compared the smoking habits of patients with peptic ulcer with those of controls who had conditions believed to be unrelated to smoking. Whilst it is true that there were fewer non-smokers among patients with ulcer than among the controls, there was no appreciable difference between the two groups of patients in respect of those who smoked 15 grams daily or more. The proportion of cigarette-smokers was higher in the ulcer group than in the controls.

Ulcer healing proceeded more favourably in 40 patients who were advised to stop smoking than in 40 who received identical treatment but were not advised to stop smoking. Those who followed the advice and stopped smoking completely did better than those who reduced it but did not stop it completely. The authors quote three recent studies of great interest in this connection. In the first study, it was found that the mortality of doctors from peptic ulcer in Britain was lowest among non-smokers and increased to a maximum among heavy smokers. In the second study, involving a larger group, the same relationship was found, but it is wisely concluded that the deaths are usually the result of perforation, bleeding or operation, and as the outcome of these complications is often dependent on the condition of the chest, the smoking may be an indirect cause through its association with chronic lung disease. This does not explain, however, the higher effect on gastric than duodenal ulcer.

In the third study which involved 1000 men aged 60-69, also reported elsewhere,[2] the study of their smoking histories showed that peptic ulcer prevalence increased from 6.6% in the non-smokers to 8.3, 9.2 and 13.0% respectively in those who smoked 1-9, 10-19, and 20 or more cigarettes daily. On the other hand, the authors do not think that smoking is an important and direct cause of peptic ulcer and remind us that smoking has undoubtedly increased in the last few decades whilst the incidence of gastric ulcer is thought to have diminished. They do feel, however, that smoking interferes with healing and helps maintain chronicity of peptic ulcer.

When looking over the truly overwhelming literature which has accumulated in recent years with regard to etiology and various other aspects of peptic ulcer, one cannot escape the feeling that of all the factors so far mentioned none is the decisive one, and that one may have to accept a multiplicity of causes for peptic ulcer. Maybe it would be more fruitful for future clinical research if we did not think of it as of one disease but divided it into several varieties according to either symptomatology or age groups. It is quite conceivable that revaluation of the various observations such as night secretion, pain-relief-pain sequence, response or lack of it to psychotherapy, etc., would follow a more understandable pattern. The idea that there are various types of peptic ulcer is not new, and Crile emphasizes that gastric ulcer and duodenal ulcer are different diseases whilst Ogilvie speaks of four different types of duodenal ulcer.

W.G.

REFERENCES

1. DOLL, R., AVERY JONES, F. AND PYGOTT, F.: *Lancet*, 1: 657, 1958.
2. BROWN, R. G., MCKEOWN, T. AND WHITFIELD, A. G. W.: *Brit. J. Prev. Soc. Med.*, 11: 62, 1957.

Canad. M. A. J.
June 15, 1958, vol. 78

Medical News in brief

TRACHEAL FENESTRATION FOR ADVANCED EMPHYSEMA

At the Annual Meeting of the American Trudeau Society in Philadelphia, Rockey and his colleagues of New York described a new method of treating advanced emphysema. They perform the operation of tracheal fenestration, creating a skin-lined communication between the neck and the trachea, guarded by air-tight external skin valves. The outer end of the tube has two skin valves in close apposition, preventing leakage of air or liquid. The valves may be manually opened for aspiration and medications. When not in use, they contract and re-establish the normal tracheal airway. Thus a means of ready and repeated access to the tracheal-bronchial tree is provided, and with its use striking results have been obtained in both wet and dry emphysema.

KANAMYCIN

At the recent meeting of the American Trudeau Society in Philadelphia three papers were read on a new Japanese antibiotic called kanamycin, derived from *Streptomyces kanamyceticus*. This antibiotic inhibits growth of human strain tubercle bacilli *in vitro* at concentrations ranging from 0.4 to 5 micrograms/ml. In experimental guinea-pig tuberculosis it has had about the same degree of beneficial action as streptomycin, and no cross-resistance has been observed between it and other antituberculous drugs. No acute or delayed toxicity was seen. However, workers at Saranac Lake have demonstrated the emergence of kanamycin-resistant strains *in vitro*. A preliminary trial in Syracuse, N.Y., gave favourable results in 12 patients with advanced pulmonary tuberculosis. They received 0.25 to 1 g. intramuscularly daily for four to six months. The agent was rapidly absorbed and rapidly excreted, and the toxicity pattern resembled that of streptomycin with kidney irritation on the maximum dose. The Syracuse observers think that kanamycin is good enough to warrant further and extensive trials.

TOLBUTAMIDE TOLERANCE TEST FOR DIABETES

A new test for diagnosis of mild diabetes is reported by the U.S. Veterans Administration, after extensive clinical evaluation at the V.A. hospital in Dallas, Texas. Sodium tolbutamide is injected into the patient's vein, and the response of the blood sugar level is analyzed 20 and 30 minutes later. Non-diabetics show a rapid decline in blood sugar level, whereas the level in diabetic patients falls much more slowly.

These results were reported by Drs. Roger H. Unger and Leonard L. Madison of the University of Texas Southwestern Medical School and the Dallas V.A. Hospital, on the basis of tests in 100 non-diabetics and 75 diabetics. According to Drs. Unger and Madison, comparison of blood sugar curves after tolbutamide injection made it possible to distinguish between diabetics and non-diabetics with an accuracy of approximately 95%. The test is based upon the presumed ability of sodium tolbutamide to stimulate the insulin-producing cells of the pancreas to release more insulin, thereby lowering the blood sugar level.

The normal pancreas would release a larger amount of insulin than the diabetic pancreas, thus accounting for the greater lowering of blood sugar level in normal subjects.

The test may provide a useful supplement to other more time-consuming tests, since it is complete in 30 minutes. It appears safe and no serious undesirable reactions have been encountered.

CANCER AND ARSENICAL TREATMENT

Recently the *Canadian Medical Association Journal* published an article by Rosset (78: 416, 1958) suggesting a relationship between prolonged arsenical treatment and carcinoma of internal organs. A further article on the same lines by Danbolt and Foss of Oslo, Norway, has also recently appeared (*Tidsskr. norske lægefor.*, 78: 275, 1958). These two observers found four patients who had previously received extensive courses of arsenic and who developed arsenical keratosis, skin carcinoma and carcinoma of internal organs (bronchial carcinoma in two cases, carcinoma of prostate and bladder in one other, and carcinoma of pancreas in the fourth). It is suggested that the cause may have been the arsenical treatment. Out of 74 patients operated on for bronchial cancer recently in the Oslo Hospital, 12 had received arsenical treatment from three to 30 years previously. It is noteworthy that in a series of 248 patients with skin disorders, 19% had previously had courses of arsenic.

PRACTICAL SIGNIFICANCE OF CYTOLOGIC EXAMINATION OF BRONCHIAL SECRETIONS

The value of cytologic examination of bronchial secretions is discussed by Kahlau (*Deutsche med. Wchnschr.*, 83: 535, 1958) on the basis of personal experience with some 7000 examinations of sputum and 500 examinations of bronchial secretions over seven years. In 57% of patients with cancer of the lung the cytologic examination was definitely positive and in another 10% the diagnosis was "probably positive". On the dark side of the picture, it has to be admitted that in 83 patients without cancer of the lung, tumour cells were diagnosed in the sputum in 13% and in another 14% the diagnosis was "probably positive". In spite of this, the author contends that in the individual case the cytologic examination is of great value, much more than the statistics indicate. He emphasizes the fact that the majority of false positives are found among patients who have some other, usually chronic lung disease, which produced metaplasia of the bronchial epithelium. The same difficulty in differentiating these metaplastic cells from carcinoma is encountered in cervical biopsies in carcinoma *in situ*.

Case reports are given to illustrate the value of this method in cancer of the lung in general and in alveolar cell carcinoma in particular. In the latter the sputum is particularly rich in tumour cells, long before the diagnosis can be established by other means. Bronchoscopy is of no value and even bronchograms are unsatisfactory in alveolar cell carcinoma.

(Continued on advertising page 42)

MEDICAL FILMS

FILMS FOR PROFESSIONAL AUDIENCES

FIVE films for professional audiences only are available from the Smith Kline & French Inter-American Corporation. They are obtainable without charge by writing directly to Smith Kline & French, Film Center, 300 Laurentian Blvd., Montreal 9, P.Q. At least four weeks' notice should be given wherever possible.

In addition, the Film Center has a number of films which are suitable for lay audiences. A "March of Medicine" Series (16 mm, B & W, sound, 30 min.) contains the following films: *Heart Disease, Cancer, The General Practitioner, Overweight, A Controlled Cross Transfusion Operation, Schizophrenia, The Arterial Graft, Ten Years after Hiroshima, We the Mentally Ill, Pathology, The Ion Knife, Alcoholism, The Lengthening Span, Child Behind the Wall, Medical Progress 56,* and *Mongana* (16 mm, colour, sound, 55 min.) Two additional films are available for lay audiences: *Man in Shadow* (16 mm, B & W, sound, 52 min.) and *The Ordeal of Thomas Moon* (16 mm, B & W, sound, 14 min.). These films are available, free of charge, to any interested medical association.

The Metabolic Insufficiency Syndrome: Diagnosis and Treatment—16 mm, Colour, Sound, 25 minutes (1956) (Available in English and French).

A medical-teaching film with product information. Reviews the process of metabolism, describes the etiology and diagnosis of metabolic insufficiency syndrome, and shows the examination and diagnosis of a typical patient and her response to treatment with a new drug—triiodothyronine.

Although directed primarily toward the general practitioners, this film should also be of interest to residents, interns, and medical students.

Mind and Medicine—16 mm, B & W, Sound, 45 minutes (1955).

This film reports on mental illness as a physical disease (as illustrated by abnormalities in carbohydrate metabolism) rather than merely a "state of mind". It demonstrates artificially induced schizophrenia in research; electroshock therapy including the use of muscle relaxants; the effect of drugs in group and individual therapy; and the use of environment as a therapeutic tool at mental hospitals.

The last section is of particular interest because of the unusual ideas and practices demonstrated at first in the Geel Colony in Belgium, where patients live in foster homes as part of a family; secondly, at Belmont Hospital in England, where patients and staff alike gather daily to discuss mutual problems, both personal and institutional; and at Warlingham Park Hospital near London where Dr. Rees outlines the advantages of his hospital's open-door policy.

The Management of Coronary Artery Disease—16 mm, B & W, Sound, 1 hour and 45 minutes.

A distinguished panel discusses the incidence of coronary artery disease in the United States compared to other countries, the causes of atherosclerosis, various methods of treatment, and prognoses for coronary patients.

A patient with a history of angina pectoris investigates the precipitating factors both emotional and physical which bring on an attack, and prescribes a regimen designed to inhibit further attacks. Eating habits, weight gain and loss reviewed. Use of œstrogens, radioactive iodine, surgery, and oxygen, is examined by panel, with opinions aired on bed and chair rest, exercise, smoking, and alcohol.

Human Gastric Function—16 mm, Colour, Sound, 18 minutes (1957).

In this teaching film, Dr. Wolf, Head of the Department of Medicine, University of Oklahoma, reports on an experimental study of "Tom". A unique patient widely known in medical circles, "Tom" had an accident in early childhood which resulted in an extensive gastric fistula. This condition allowed study of the mucosa and observation of secretory action and gastric motility under various conditions. The investigators were able to gain insight into the stomach's complex responses to different psychological states and stresses. The film is a partial record of 15 years' continuous study of "Tom's" fistula. From 1941 to 1952 this study was carried out in collaboration with Dr. Harold G. Wolff of Cornell University Medical College. The final phases of research, from 1952 to 1956, were performed at the Oklahoma Medical Research Foundation, Oklahoma City.

The Physician and Emotional Disturbance—16 mm, B & W, 54 minutes (1957).

This film is the kinescope of a program shown simultaneously at five state medical association meetings on closed-circuit television. The program was presented in cooperation with the American Medical Association. Discussion centres on the role of the general practitioner in treating mild emotional disturbances or psychosomatic conditions. Motion-picture scenes of a patient's interview with his physician are included, and the interview is discussed by the panel. The panel also answers questions from the participating state meetings. Members of the panel include Dr. Leo H. Bartemeier as moderator, with Drs. C. Knight Aldrich, E. Irving Baumgartner, C. Hardin Branch and Andrew S. Tomb as participants.

The Buccal Use of Varidase—Sound, Colour, 25 minutes.

This motion picture describing the medical applications of Buccal Varidase (streptokinase-streptodornase) tablets is available from Lederle of Canada, a division of Cyanamid of Canada Limited. The film shows how the drug is used in management of inflammation and swelling associated with trauma and infection. In addition to demonstrating the physiology of streptokinase and the route of buccal absorption, the film presents clinical cases in which Buccal Varidase was used.

Prints of the film can be obtained by writing to the film library of Lederle of Canada, 5550 Royalmount Avenue, Montreal 16, P.Q. Requests should be made at least three weeks in advance of the proposed showing.

ANATOMY

Tumour Cells and Macrophages in Tissue Cultures—1929; Silent; B & W; 16 minutes.

Produced by Dr. Warren H. Lewis, Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.

Description.—A record-instructional film, demonstrating the behaviour of tumour cells and macrophages in tissue culture.

Appraisal (1947)*.—Although there is insufficient explanation in the subtitles, the fine points of cell division are beautifully shown. It is difficult to specify for which groups the film should be recommended, as it requires a running explanatory commentary by the lecturer. Should be suitable for specialists in the subject matter and for medical students in the clinical years. Inappropriate for other audiences.

Availability.—National Medical and Biological Film Library ($1.50). Purchase from Wistar Institute of Anatomy and Biology, 36th Street and Woodland Avenue, Philadelphia 4, Pa.

---

*The evaluation was prepared by Canadian specialists in the subject of the film, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

(To be continued)

Canad. M. A. J.
June 15, 1958, vol. 78

Men and Books

GEORGE LYMAN DUFF: IN MEMORIAM
FIRST ANNUAL GEORGE LYMAN DUFF MEMORIAL LECTURE*

WILLIAM BOYD, M.D., F.R.C.P.(Lond.), F.R.C.S.[C],† *Willowdale, Ont.*

IT IS CUSTOMARY for the speaker at a memorial lecture to devote a few words to the man who is being honoured, and then to address himself to a subject in which his audience is particularly interested and on which he himself is an authority. In the present instance that subject should, of course, be arteriosclerosis, but unfortunately for me there is not a member of this audience who does not know much more about the subject than I do. I do not wish to insult your intelligence or waste your time, so I shall confine myself to Lyman Duff, and then add a few words on men and the Man.

Biographic data in detail are a weariness to the flesh, so I shall pick out only a few points of significance. Duff was a Canadian who was educated at the University of Toronto. He took the Bachelor of Arts degree in Biology and the Medical Sciences in 1926, working during the summer holidays at a marine biology laboratory. So when he wrote his Master of Arts thesis he chose as a subject "Factors involved in the production of annual zones in the scales of the cod". This was when he was still an undergraduate student in the medical course with a very full curriculum. I wonder what sort of showing any of us would have made with that subject. I mention this to indicate the breadth of his interest in biology. In 1929 he graduated M.D. at Toronto, winning the David Dunlap Memorial Prize in psychology and psychiatry, another point worthy of our consideration.

Then began his all-important postgraduate career, during which he was to be influenced by men of outstanding ability and personality. The first of these was his professor of pathology, Oskar Klotz, and it was during the two years he spent with Klotz that he acquired his lifelong interest in arteriosclerosis. Surely it is significant that Klotz himself wrote his first paper on the subject of arteriosclerosis when he was resident in pathology at McGill University under Adami, later becoming a world authority on the subject, only to be followed in due course by Duff himself. I believe that Adami brought his interest in arteriosclerosis to McGill from Cambridge where he was a pupil of Roy, in whom the seed of interest in the subject was first sown in Germany by Cohnheim, the supreme experimentalist. The strong influence of Cohnheim was ever after very clearly apparent in Roy's line of thought, in his work, and in his teaching. Here we have an example of a theme I shall touch on later, namely the profound influence which a master of a subject can have on a disciple.

Duff then moved on a fellowship to Johns Hopkins, where he was exposed to fresh stimulation from W. G. MacCallum and Arnold Rich, and completed his thesis for the Ph.D. degree of the University of Toronto, choosing as his subject "Experimental studies upon arteriosclerosis". After three years at the Johns Hopkins he returned to Toronto, first as Lecturer in Pathology and then as Assistant Professor. During the last two of his four years on the staff at Toronto, I had the good fortune and great pleasure of being associated with him, and had full opportunity to appreciate his brilliance of mind and charm of character. I attended many of his lectures to students on general pathology, taking many notes, somewhat to the amusement of the class. I still use some of his graphic expressions such as "the streaming blood" to indicate the circulatory condition necessary for thrombosis as opposed to clotting.

In 1939 he was appointed Strathcona Professor of Pathology at McGill University. Here, as you may well imagine, he encouraged and stimulated research in his department, acting as a catalyst for the young minds whom he soon collected around him from far and near. He remained true to his first love, arteriosclerosis, but also made notable contributions to our knowledge of pancreatic tumours, collagen diseases, the demonstration of the renal vasculature by neoprene casts, and many other subjects.

Ten years later he was appointed Dean of Medicine, and had now to divide his time between research and medical education in which he became keenly interested until his untimely death from bronchogenic carcinoma at the early age of 52. One who was closely associated with him in the work of the faculty writes of the judicial frame of his mind, perhaps inherited from his distinguished uncle, Sir Lyman Duff, Chief Justice of Canada. "Its chief characteristics were patience, complete impartiality and fairness, a wide outlook, and an entire absence of pet ideas and theories. He gave a fair hearing to all sides. Yet, having weighed a question, he could come to a decision and present it cogently and convincingly. Nor was it easy to move him once he had made up his mind. He was neither overawed by those in authority nor neglectful of the opinion of lesser folk. Criticism and dissent neither irritated him nor awakened the slightest resentment, and he was always ready to meet an objection with a reasonable compromise." Is not that a picture of a dean that any one of us would be happy to serve under? Those of you who have suffered from deans of a very different calibre will know what I mean.

When a man passes from us, no matter how distinguished he may have been, his friends remember him not chiefly for his works but rather because of his character, the breadth of his influence, and his friendships. So it was with Lyman Duff, and those among you who knew him well can best appreciate what I mean. When he died, it was as if a fire had gone out and the world was a colder place. I still remember the warmth of the old-fashioned party which Isobel and he gave for my wife and myself when first we came to Toronto. I call it old-fashioned not on account of its style but because of the superb character of the Old-fashioneds which Duffy, as we affectionately called him, mixed with his own skilled hands. The quality of the man was perhaps best demonstrated by

*Delivered at the Eleventh Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, Illinois, November 3, 1957.

his extremely happy family life and by his attitude to his final illness.

> "Life is mostly froth and bubble,
> Two things stand like stone:
> Kindness in another's trouble,
> Courage in one's own."

He was a chief whom any of the younger amongst you would have wished to serve under.

And that leads me to say a few words regarding a Man as opposed to men. In this respect it is interesting to compare the last century with the present one. The 19th century was a century of individuals who, either by their personality, their deeds or their thoughts, made a tremendous impact on the men with whom they came in contact. Think of Napoleon on land and Nelson on the sea, Ludwig van Beethoven and Richard Wagner, both the quintessence of individualism, Karl Marx and Charles Darwin, Gregor Mendel and Claude Bernard, Louis Pasteur and Rudolph Virchow. These men, who did such epoch-making things, were individualists, not members of a team or union. In the present century the trend seems to be to reduce everyone to a common and uniform level. Even in our schools we tend to discourage the brilliant and bring forward the dull. How different from the outlook of Winston Churchill, himself, like Lincoln, the supreme example of an individualist, who wrote: "It is only when young men are really thirsty for knowledge, longing to hear about things, that they should be allowed to go to the university. It should be a favour, a coveted privilege, only to be given to those who had already proved their worth." This is the age of the committee, the trade union, the business combine. Even the great criminals have lost colour and sparkle. Our great discovery is that if you want to get things done you must form a team and organize a production line. Such organization was needed to produce sufficient power to push Sputnik into outer space and become a satellite. It is required for the production of an automobile or an aeroplane. It is apparently necessary for the writing of a group textbook on medicine or pathology or even one on the liver. When we look at an article in one of our medical journals and see the names of eight authors, male and female, M.D. and Ph.D., we wonder who did the thinking and the work, and who really wrote the paper. Do not let us forget Napoleon's great saying: "In war, it is not men but the Man that counts." In the 19th century an article was signed William Osler, or Joseph Lister, or John Bright, or Louis Pasteur, or Claude Bernard, and we knew where we were. But now it is different.

The great man, as opposed to a member of a great team, may be great in research, he may be great as a writer, or he may be great as a teacher, a source and centre of inspiration. William Osler made no outstanding discoveries, but everyone who came in close contact with him became a different man. Johannes Müller made his name as an anatomist and physiologist, but he was also an inspiring teacher, he was worshipped by his students and assistants, and he will live in medical history as the man who kindled the flame in Henle, the anatomist, in Virchow, the father of modern pathology, and in Helmholtz, the supreme combination of physiologist and physicist.

We have seen how Adami sowed the seed of research on arteriosclerosis in Oskar Klotz, how Adami received that seed from Roy, and he in turn from Cohnheim, how Klotz passed on seed to Lyman Duff, and Duff in turn to those around and under him, like Gardner McMillan who succeeded him at McGill and who is with us today. And thus the golden thread can be traced throughout the years, but it stretches from man to man, not from group to group. Let our young people remember that even in these days when organization reigns supreme, when standardization has become a fetish, and to be too outstanding is to be rather queer and therefore suspect, there is still room for the rare man who can put his spell on you and change the whole course of your future life.

40 Arjay Crescent,
Willowdale, Ont.

GENERAL PRACTICE

CUTANEOUS MALIGNANCIES OF THE FACE*

M. S. MILLER, M.D., F.A.C.S., F.I.C.S.,
Calgary, Alta.

I BECAME interested in cutaneous malignant tumours of the face because: (1) Carcinoma of the skin is the most common form of cancer. (2) Skin cancer is the most curable, yet comprises 6% of all cancer deaths. (3) Cancer of the face can be detected early, since it is in an exposed part of the body. We must always be on the lookout for these lesions; no matter what the patient comes in for, look at the face first. (4) Carcinoma of the face can almost always be cured if diagnosed early and treated correctly.

It should be classified as:

A. Malignant lesions
   - Basal cell carcinoma
   - Epidermoid carcinoma
   - Malignant melanoma

B. Pre-malignant lesions
   - Senile keratosis
   - Leukoplakia

MALIGNANT LESIONS

Most cancers of the face are basal cell tumours, the notable exception being that of the lip, which is of epidermoid type.

Basal cell carcinoma (adnexal carcinoma or rodent ulcer): These comprise most cancers of the face, and usually occur in the mid one-third of the face (i.e. below the eye and above the mouth). They occur on the face, eyelids, nose and external ear. The characteristic feature is slow growth; they may take months or years to grow. They do not metastasize but cause local erosion. Basal cell tumours may "iceberg" under the skin, and may

*Read at the Annual Meeting of the Canadian Otolaryngological Society, Banff, Alta., June 19, 1957.

Canad. M. A. J.
June 15, 1958, vol. 78

not be readily detectable on clinical inspection. This is of great importance in treatment and prognosis. In these cases recurrences may be due to incomplete removal.

Basi-squamous carcinoma: Occasionally, a basal cell tumour may become an epidermoid type. Sudden enlargement of a slow-growing tumour should arouse suspicion of this basi-squamous type. The management of this type is that of an epidermoid carcinoma.

Epidermoid carcinoma (squamous epithelioma and malignant epithelioma): Any growing non-pigmented skin lesion should be suspected of epidermoid carcinoma unless proven otherwise. The tumour starts as a thickening of skin or a nodule; it is most curable at this stage. Later it may ulcerate, then metastasize. For this reason it is more dangerous than a basal cell tumour.

Malignant melanoma: This is sometimes called the black death, because of its poor prognosis. Where suspicion arises, wide excision and microscopic examination are necessary. If a mole is subjected to recurrent trauma, excise it. If it is not in an area of irritation, leave it alone unless it has to be excised for cosmetic reasons. The majority of moles are harmless. They should never be curetted, fulgurated or irradiated.

PRE-MALIGNANT LESIONS

Any sore that does not heal within four weeks may be pre-cancerous.

Senile keratosis: This is the commonest pre-cancerous lesion. It occurs in older persons, especially those exposed to sun and dust, and is commonest in blonde people. Every lesion of senile keratosis should be destroyed, because 20% or more turn malignant. It should always be excised, no matter what its size, or treated by a shaving operation. Irradiation is contraindicated, because the lesion is due to skin exposure to chronic irritation. *Seborrhœic keratosis* is a benign neoplasm; it is greasy and usually found in seborrhœic skin, whereas senile keratosis is flat, dry and scaly.

Leukoplakia: Any rough, scaly or bleeding lesion of the lower lip of over one month's duration should be removed. The minimum procedure is surgical shaving of the mucosa.

DIAGNOSIS OF FACIAL SKIN TUMOURS

There is only one method of diagnosis—by excision and microscopic section. Never watch a small tumour grow, for the best results are obtained early.

Excision and rapid section where possible is better than excision biopsy alone; not only can treatment be applied immediately, but it can be seen whether the tumour has been completely removed, well beyond its microscopic margin. If the specimen is too small for rapid section, it does no harm to wait a few days for the report on paraffin sections.

Do not try to make a diagnosis of malignancy on the gross appearance of the tumour. Never cauterize a suspicious growth or use irradiation without a microscopic examination first.

Biopsy: Complete excision is better than a punch biopsy or excision of a small section of the growth. The latter may not tell the whole story. Never use the cautery knife; use a cold knife so that the tissue will not be burned. Use of local anæsthesia has been condemned, as likely to spread the tumour, but I do not think that this has ever been confirmed. Unless the surgeon can undertake the treatment, should microscopic section prove the tumour to be malignant, he *should not do the biopsy.*

TREATMENT

The initial treatment is the golden one. Once the tumour recurs, the problem is no longer simple. Treatment implies the early recognition and complete destruction of the tumour the first time. It makes no difference whether surgery or irradiation is used, provided the tumour is destroyed with the best possible *cosmetic result.* Both types of treatment are destructive and the therapy must be radical.

1. *Excision with scalpel:* This is the best method in good surgical hands. It is contraindicated only when a good cosmetic result is impossible. Incisions are made along Langer's lines, and at least 5 mm. beyond the margin is excised, with use of a magnifying glass. This technique is best in old people, and wherever the skin is flaccid and the edges can be brought easily together. The excision must not only be wide enough, but deep enough.

2. *Electrosurgical excision (surgical diathermy):* This is simple and gives a good cosmetic result. Under good illumination and a magnifying glass, outline the area to be excised with methylene blue or indelible pencil, before injecting the local anæsthetic. Excise the area, and examine the specimen microscopically. If the tumour is malignant, apply diathermy to the edges and base for 3 mm. beyond the original excision. The wound should be allowed to heal by granulation tissue. It may be left exposed or covered with a Vaseline dressing. It heals by granulation tissue, and the cosmetic result is good. The method is used for moderate-sized basal and epidermoid carcinoma, only in areas over cartilage, as on the ear and nose. If the tumour is large, wide excision is necessary.

Electrocoagulation is mentioned only to be condemned. It should never be used, especially when a diagnosis has not been made. It may be used occasionally in senile keratosis.

3. *X-ray therapy:* When surgery will cause deformity, radiation treatment is indicated. Avoid using it over cartilage or bone, as it may cause sloughing. Never use it in pre-cancerous lesions such as senile keratosis, scars, leukoplakia, roentgen dermatitis or lupus. Never use it if the patient has had previous irradiation. Inadequate irradiation makes the tumour more resistant. It is contraindicated if the lesion is fixed, and in the elderly. Both surgery and irradiation are highly successful in basal cell carcinoma. The one giving the best cosmetic result and also destroying the tumour is the method of choice. In epidermoid carcinoma, I use surgery in all cases, unless the tumour is too large to excise. The treatment will thus depend on the *size* and *location* of the growth.

Size: A small lesion (up to 2.5 cm. in diameter) should be excised. For a large lesion, if a reasonable cosmetic result will be obtained, surgical excision is the method of choice. If surgery will cause much deformity, irradiation is indicated.

Location: If the tumour is near vital structures, for example, on the bulbar conjunction, it is impossible to shield the eye from the x-rays. A tumour here or on the tarsus should be excised. On the other hand, if the tumour is at the inner or outer canthus, the eye can be protected and irradiation given. For tumours of the nose and ear, over cartilage, use surgical diathermy.

Whenever epidermoid carcinoma is reported on section, palpate the site of lymph drainage for secondary lymph nodes. If palpable glands are present, excise them.

Recurrence

Recurrence means inadequate treatment, irrespective of what treatment was used. The greatest cause of failure is insufficient irradiation or an inadequate operation. It is not the type of treatment, but the thoroughness that counts. An expert radiotherapist is better than a poor surgeon. A capable surgeon is better than a poor radiotherapist. A man qualified to do a good plastic repair will make a much wider excision. Removal must be complete on the primary attempt.

Routine Management

Admit to hospital or treat the patient as an outpatient at the hospital. Excise at least 5 mm. beyond the edge of the growth and study a rapid section. If the tumour is malignant, destroy it by the method that gives the best cosmetic result.

Summary

Cancer of the face is one of the most common forms of malignant disease and, although one of the most curable, has too high a death rate at the present time.

Early recognition of the tumour and complete removal the first time is essential.

Any sore that does not heal, or any growing lesion, must be excised completely and examined microscopically.

The tumour must be completely destroyed in the primary attempt, whether surgery or irradiation is used. The method of choice is the one that completely destroys the tumour, while at the same time allowing a good cosmetic result.

References

1. Conway, H.: *Surg. Gynec. & Obst.*, 74: 449, 1942.
2. Kitlowski, E. A.: *J. Internat. Coll. Surg.*, 23: 447, 1955.
3. New, G. B.: *S. Clin. N. America*, Aug. 1941.
4. *Idem*: *Laryngoscope*, 59: 731, 1949.
5. Straith, C. L.: *Plastic and Reconst. Surg.*, 3: 262, 1948.
6. Hammar, L. M.: *Minnesota Med.*, 35: 1135, 1952.
7. Michelson, H. E.: *J. A. M. A.*, 136: 683, 1948.
8. Webster, J. P.: *Arch. Dermat. & Syph.*, 35: 573, 1946.
9. Wolfe, J. J.: *Am. J. Surg.*, 87: 663, 1954.

202 Hart Bldg.,
227-7th Ave. West.

MEDICO-LEGAL

THE VALUE OF TIME

T. L. FISHER, M.D.,* *Ottawa*

Perhaps the ends of justice are better served by the pace at which the law moves; perhaps everyone would be worse off did it move, not more quickly but less slowly; it may very well be that there are fewer law suits because tempers have time to cool, because judgment is given time to reassert itself, because sheer weariness and frustration prompt claimants to drop claims: whatever the reason, the courts, in civil cases, move slowly, ponderously, sometimes meticulously, oftentimes with an inevitability and irresistibility which are magnified and made frightening by the sluggish progress. Distressing as this is to the doctor who is the victim of the proceedings, he should not object too strenuously because in the majority of cases time works on the side of the doctor. The natural tendency for illness to get better, for disability to decrease, for healing to occur, for function to be restored, any of these or all of them in varying proportions have saved more than one doctor from the wrath of a patient who, when he first recognized the incompleteness of his recovery, failed to recognize that nothing better was possible and decided to take legal action against the unfortunate doctor he thought the cause of his trouble.

One thing is said at some time during the progress of an action against him by nearly every doctor to whom the Canadian Medical Protective Association extends assistance: What can be done to hurry a decision? The suspense, the waiting for the case to develop, the knowledge that at some time in the unknown future this thing is going to happen, is in all probability more strain and harder to bear than the trial itself when it comes. The fact that so many cases are dropped before they ever reach court does not lessen the strain. The following case is different from many others only in that it had a clear-cut end; many just languish without ending.

In December 1951, a doctor had to remove a fibrosarcoma from the skin of the left buttock of a patient and performed a plastic procedure to repair the resulting defect; 24 hours later the patient had to have another operation to stop hæmorrhage; three weeks later further skin-grafting was done. For all three operations the patient had to be on his side with the lower arm on a board out at right angles from the operating table. After the last operation he complained of pain in his right shoulder and arm, and within a week paralysis of some of the muscles of the arm developed because, it was thought, the brachial plexus had been stretched during the last operation. The patient complained almost immediately and his complaints increased until in August 1952, he retained a solicitor who asked the doctor to go to his office to discuss the matter. The doctor went, foolishly, apparently without realization that the solicitor, having been retained by the patient, could be interested only in gaining information from the doctor to bolster a case against him.

---

*Secretary-Treasurer, Canadian Medical Protective Association.

Canad. M. A. J.
June 15, 1958, vol. 78

Shortly thereafter the solicitor suggested that the doctor retain a lawyer who could enter into negotiations for a settlement. This the doctor refused to do, and in November a writ of summons was served on the doctor.

At that time a solicitor was retained to represent the doctor, an appearance was entered and both doctor and solicitor awaited the statement of claim. In May 1953, the plaintiff's solicitor said that his client was not anxious to press the claim against the doctor but was still suffering disability and felt entitled to compensation; that he was prepared to be very reasonable about his claim and that if some settlement were not reached promptly the action would be pressed; the plaintiff was willing to settle for $2000 plus legal costs. This offer of settlement was declined.

In December of 1953—two years, it will be noted, after the alleged injury was received—the doctor's solicitor reported that the matter was at a standstill and in July 1954, though no further official action had been taken, the doctor's solicitor reported that there had been overtures with a view to settlement on more than one occasion, at the last of which it was suggested that the sum of $500 would purchase a release.

In December 1954—three years after the first complaints—it was reported that nothing further had been done and that, though uncertain, it was likely nothing further would be done. Meanwhile during 1953 and 1954 the patient had made a fairly good recovery which allowed the surmise that he might not pursue the litigation further. In February 1955, the plaintiff's solicitor said that he had instructions to discontinue the action if the doctor would not tax costs against the plaintiff. On February 4, notice of discontinuance of the action was filed, and only then could the case be considered finished.

Three years of suspense had elapsed from the time of the first complaint until the doctor could feel free of worry about the case.

The timing of the events is fairly typical. It differs from a majority of cases only in that it came to a demonstrable end with the filing of the notice of discontinuance; it differs from a minority of cases only in that it did not come to trial.

Several things which doctors should do and some they should not do occurred. This doctor gave his patient a fair, a factual and a concise explanation of the cause of the trouble as soon as the first complaint was voiced. This was proper. This doctor went to the office of the patient's solicitor when he was requested to do so to discuss the case, in effect to expose himself to an examination to which he could supply no rebuttal. This was a wrong thing to do; he might easily have prejudiced his own case. Soon thereafter the doctor notified his defence organization and accepted instruction from them—a correct thing to have done though it should have been done sooner, as soon as he knew there was a complaint or at the latest when the complaint began to take shape as a threat. The doctor did not put any pressure on his defence organization to hurry the action—properly he awaited developments.

As it does in so many cases, time acted in this doctor's favour. Had the case come to trial while the patient was still paralyzed, a favourable outcome might have been harder to obtain.

MEDICAL ECONOMICS

ARE THERE TOO MANY DOCTORS IN CANADA?

In recent months the medical profession in Canada has been confronted with two conflicting, authoritative statements about present and projected needs for physicians.

The Dominion Council of Health, comprised mainly of our deputy ministers of health, has indicated a need for more physicians and other health personnel because "of an expanding health service, the growth of the population of Canada, and the changing age composition of that population. . . ."[1]

In contradistinction, Dr. Rolph Struthers, a noted physician in academic and research fields, has stated that "it would appear that our [physician] needs are being adequately met, and that it is time to call a halt to the expansion of medical schools, both as regards their numbers and the size of classes admitted thereto. . . ."[2]

Our interest is the assessment of these conflicting opinions. To do so, we must consider the many variable factors which combine to express the effective demand for medical services and to control the supply of new physicians. Most of these factors are not susceptible of precise analysis.

However, the demand for services is in many ways directly related to population growth and age distribution. The report of the Gordon Commission on Canada's Economic Prospects envisages a population increase, from natural growth and net immigration, approximating 2% per year. Thus, to maintain our present population-physician ratio, in 1965 we will require 25% more physicians than in 1955, and in 1975 our requirements will be 54% greater than in 1955.

These requirements, imposed by population trends, do not encompass all factors which influence the demand for medical services. They presuppose the continuing adequacy of our present population-physician ratio. One may well contend that this is a valid assumption, as the ratio has not varied significantly during the past 60 years. It is, however, interesting to note that this net result reflects the aggregate of diverse changes in many variable factors—scientific and technological advances, the shift in emphasis to preventive medicine, public awareness of their medical requirements, improvements in transportation facilities, increases in hospital beds and technical assistance, and changes in the personnel and other facilities available in the doctor's office.

It would not be prudent to try to forecast the precise effect of future changes in these and other factors which influence the demand for services and the facility of meeting this demand. It is sufficient to say that we shall be fortunate indeed if the net change allows a physician to provide care for a larger group of people.

Two separate yet related factors tend to negate this supposition. We have sufficient statistical information to state that the insurance mechanism, whether medical or hospital, private or state-supported, tends to create a new demand and to increase the existing demand. Certainly an assessment of our future must countenance a broader application of this mode of payment.

A second factor outweighs other considerations. It is the level of economic prosperity. Some countries, not as fortunate as we in terms of population-physician ratio, do not experience the demand for medical services which can be provided by their physicians. We observe the situation where the output of medical schools considerably exceeds the capacity of a country to utilize physicians' services, with two alternatives presented to new graduates—emigration or staying at home and engaging in competitive practices for a place in a body of physicians facing a declining economic future. We are prone to consider these countries as outstanding examples of the problems attendant upon an over-supply of physicians. In fact, in most instances, the basic concern is not over-supply by our standards, but rather lack of demand due to economic circumstances.

The reasons are economic. Each physician must receive some economic reward. Whether payment is made by the patient or by the state, the amount of money available for his income is determined by the level of economic activity. This phenomenon is demonstrated in Canada. Provincial population-physician ratios decrease as per capita incomes rise. This trend supports the observation that as our real income increases, the public is willing to apportion an increasing proportion of income to meet the costs of medical services. This relationship is not to be interpreted as evidence of a mercenary attitude on the part of doctors, but rather as due to the fact that the economic conditions of a region have a direct relationship to the demands for medical services. Today, as Canada stands on the threshold of a tremendous future we should predict with confidence that Canadians will express an increasing demand for medical services.

An assessment of these factors leads us to predict, conservatively, an increase in demand approximating 2.5% per year in the near-term, rising to 3% per year on a long-term basis. As the estimate of practising physicians in 1955 approximated 16,000, we must attain a net increase exceeding 400 new physicians each year.

To meet this objective we must make allowances for the replacement of physician losses due to death and retirement. It is difficult to establish a precise factor for attrition, as adequate statistics are not available. Also, the component which is attributable to retirement is of greater importance than the component representing losses due to death. Retirement data are much less predictable than mortality rates, since factors influencing retirement are in many instances economic.

Dr. Struthers, in his article, suggests an attrition factor of 3%. While we cannot agree with the mathematical basis used to establish this factor, we must admit that, on a near-term basis, his prediction may be substantially correct. 1951 is the last year for which we have sufficient information to make reliable assumptions. In this year, the average physician's age was 44 and the average retirement age was approximately 71. This indicates an average work expectancy of 25 years and an attrition factor of 4%.

In the seven-year interval we would expect certain changes in these two components which would tend to reduce the attrition factor. In 1958, because of a substantial influx of young graduates, the average physician's age should be significantly lower—perhaps 41. This would presuppose a longer work expectancy. The average retirement age should be higher—perhaps 72—as a result of the persistent inflationary trend which we have experienced during this period. If our estimates of these changes are correct, the present attrition factor approximates 3.5%.

We have emphasized that this should be considered a near-term forecast. Certain factors should, on a long-term basis, significantly reduce the average retirement age. Inflation is, to a degree, controlled and one does not envisage a repetition of the excesses of the early fifties. Also, tax changes allowing retirement planning should have a marked effect. It is interesting to review our correspondence with younger participants in the Canadian Medical Retirement Savings Plan—indicating that planning is related to retirement at ages 55 and 60 and, at the latest, age 65. As an offsetting factor the average age of all Canadian physicians will be lower. It is, however, difficult to significantly reduce this average age below 41.

We would therefore suggest an attrition factor of 3.5% in 1958, rising gradually to 4% in 1970-75. This factor combined with our estimates of increased demand suggests a near-term requirement for new physicians equal to 6% of the present active civilian physician population, rising in 15-20 years to an annual requirement equal to 7% of the then-existing physician population.

Are our Canadian medical schools meeting present demand? They are not! If the total number of graduates remained in Canada to practise medicine, we would come close to meeting present requirements. However, emigration and the outflow of Canadian-trained foreign nationals substantially impair our efforts.

How is the demand being met? Present demand is being met by an unprecedented rate of immigration. During the period 1952-56, 3410 Canadian-trained graduates successfully completed Medical Council of Canada examinations. During the same period, 1440 British and foreign-trained physicians successfully completed the same examinations. In addition, an undetermined number of British graduates immigrated to the six reciprocating Canadian provinces which do not require the formality of Medical Council examinations.

Can existing facilities meet our future needs? Certainly the present output of our Canadian universities cannot. Our present facilities in large manner determine the number of medical graduates in 1965. Some small increments may be expected, but it is unlikely that the total number of graduates in 1965 will greatly exceed 950. After allowances are made for total emigration, the number we will retain will approximate 720. This situation may improve somewhat as a result of a trend toward mandatory internship in approved Canadian hospitals.

If, as we confidently estimate, the total number of active physicians will exceed 20,000 in 1965, our minimum requirement at that time suggests a need for 1200 new physicians. Can we count on or countenance a situation requiring almost 500 immigrant physicians each year?

There is, of course, another and likely way in which any deficit would be met. The demand would encourage physicians, planning retirement, to continue the active practice of medicine. This could substantially reduce our requirement for new physicians.

Canad. M. A. J.
June 15, 1958, vol. 78

However, if the result were to reduce our requirements to 5%, our need of more than 1000 new physicians in 1965 must envisage a substantial immigration factor.

If we consider it prudent to pursue a course which anticipates maintenance of present rates of emigration and immigration, we must carefully consider those variables upon which these rates are dependent.

It is unlikely that our rate of emigration will be substantially reduced. The physician entering practice in the United States will benefit from the higher standard of living, and he may be more certain than we of his medical political environment. At the present time American medical schools are not graduating a sufficient supply of new physicians to maintain present population-physician ratios. As a consequence, opportunities will continue to exist. Rather than expect any reduction in emigration, we may confidently expect an increase if any suggestion of our government indicates to our young graduates that the practice of medicine in Canada may be less attractive than present circumstances dictate.

In contradistinction, our rate of immigration is dependent upon the maintenance of attractive conditions of practice in Canada and the continuance of dissatisfaction or lack of opportunity in the countries from which we draw our medical reserves. For the next two years we will be assimilating a large number of Hungarian physicians, but beyond that point it would appear that our rate of immigration will be dependent upon the excess of British-trained physicians, who may, of course, decide to practise in other parts of the world rather than in Canada.

REFERENCES

1. Resolution of Dominion Council of Health transmitted to the Executive Committee.
2. STRUTHERS, R. R.: *Canad. M. A. J.*, 78: 480, 1958.

MISCELLANY

THE McGILL DIPLOMA COURSE IN ANÆSTHESIA

The McGill Diploma Course in Anæsthesia was started by Dr. Wesley Bourne, assisted by Dr. Harold Griffith, Dr. Digby Leigh and other members of the McGill Faculty. The object is to train anæsthetists, both from the practical and academic points of view, and to prepare them for the Canadian certification examination and other higher qualifications. If the course is satisfactorily completed, the candidate receives a diploma from McGill University.

The course, while remaining substantially the same, has been modified to keep abreast of the times. Many candidates have been successfully trained for Canadian certification, Quebec Province certification, the Fellowship of the Royal College of Canada, the Fellowship of the American College of Anesthesiologists and for the American Boards.

The course lasts three years. Credit may be given up to one year for appointments previously held elsewhere. Candidates, once enrolled, may under certain circumstances spend one of the three years at another centre, provided this meets with the approval of the chairman of the department. In both of these instances the postgraduate student is eligible for his diploma.

Each student is assigned for clinical work to one of the participating hospitals. Having spent six to twelve months in the hospital to which he was first posted, the student then spends six months in turn in a number of hospitals within this framework. Some of these hospitals are specialized while others are general. The result is a well-diversified practical teaching program.

During the university year, lectures and demonstrations are given by members of the Departments of Anatomy, Physiology, Pharmacology and Biochemistry. The pattern which these sessions take is fashioned by discussions between the senior anæsthetists and the academic staff. Examinations in these subjects may be required to qualify for the diploma.

During each appointment of six months, the resident on this course is directed by the staff members of the particular hospital where he is serving his residency. In addition, he attends seminars once a week which are organized for the group as a whole. The seminars are planned to fit the training of the student; for instance, during the first and second years they tend to be more practical while in the final year emphasis is placed on the theoretical side of the specialty.

Every Monday evening a meeting is held for all the anæsthetists in the city and any visitors who wish to attend. The students on the course are advised to be present. At these meetings there may be a guest speaker or there may be reports of interesting cases. At each meeting one of the members of the Diploma Course reads a specially prepared essay. These essays form one of the requirements of the course, the preparation of which teaches the use of the library and the critical appraisal of the literature, while the delivery is useful experience in public speaking. A third type of study, that of reviewing the literature, is encouraged at each hospital. Some hospitals devote special study periods to this and all have excellent library facilities.

Research Work

Within the Department of Anæsthesia at McGill University is an Anæsthesia Research Department generously financed by the Wellcome Trust. This department is directed by Professor J. G. Robson, who plays an important part in the academic teaching of members of the course. Those especially interested may gain appointments for one or two years under Professor Robson's direction in order to learn methods of research work. Professor Robson is always available to advise and help in the various research projects in progress in the departments of anæsthesia at the different hospitals.

Remuneration is the responsibility of the hospital to which the students are assigned. As a general rule the salary accepted is that suggested by those who direct the course, namely on the scale of $150 per month during the first year, $200 per month during the second and $250 per month during the third year. From this sum is usually deducted $50 per month in the case of those who actually live in the hospital.

Should it happen that the resident's third year on the course is his final year before examination, he can make his own private arrangements with the hospital authorities with whom he is currently working.

Holidays

Each student receives at least two weeks' holiday each year between the months of July and December. Other vacation periods are planned on an individual basis with the head of the department to which the student is assigned.

Fees

The fee for the course is $155. This covers the cost of the basic science sessions. In addition there is an annual registration fee of $10. Each student must register annually with the Medical Faculty and the University Registrar. Applications should be addressed to: Dr. R. G. B. Gilbert, Chairman, Department of Anæsthesia, McGill University, Montreal Neurological Institute, 3801 University Street, Montreal 2, Quebec.

UNRWA'S HEALTH SERVICES FOR THE ARAB REFUGEES

One of the tragic results of the 1948 war in Palestine has been the miserable plight of the several hundred thousand Arabs who then left their homes to take refuge in neighbouring Jordan, Lebanon, Syria and the Gaza Strip. Today the majority of these people still live in the same places where back in 1948 they dropped hungry and destitute, awaiting what little relief the local Arab governments could scrape together to help them.

As the weeks following their exodus stretched into months and the immediate expectation of their early return to their homes was not realized, it became apparent that more organized relief was essential if a major human catastrophe were to be avoided. Already desperate appeals were pouring in to stem what could have developed into serious epidemics of dysentery, typhoid, smallpox, typhus and relapsing fever when UNRPR (United Nations Relief for Palestine Refugees) was set up in 1949 to carry out an organized relief program with the aid of the International Committee of the Red Cross, the League of the Red Cross Societies and the American Friends Service Committee.

The danger to health was one of the major problems. A whole nation in exile was living under primitive conditions in open fields, mosques, caves and rickety tents. Small health teams were organized by a WHO specialist to meet the emergency. In the past decade, they have developed into an efficient health force serving nearly a million refugees now living in camps, towns and villages scattered over 100,000 square miles in four different countries. UNRWA (United Nations Relief and Works Agency), which took over relief activities from UNRPR in May 1950, is now spending at the rate of five million dollars a year on its health program alone. This health program is operated by more than 3500 employees, mostly Palestinian Arabs. They include 120 doctors and dentists, over 100 nurses, and more than 350 nursing auxiliaries and midwives. More than 1300 persons are employed in the camp sanitation services, and over 1000 on supplementary feeding and milk distribution. The technical direction of the health program administered by UNRWA remains the responsibility of WHO.

Preventive medicine given priority

The unsatisfactory living conditions of the refugees in an area like the Middle East which is especially open to epidemics have prompted UNRWA to give special emphasis to preventive measures in its over-all health program.

Under the supervision of a sanitary engineer seconded by WHO, strict sanitation measures are applied in all camps. These include the provision of a clean water supply, an efficient garbage disposal system, and proper sewage arrangements. Flies and other insects which help in spreading disease are combated through regular spraying with a variety of insecticides.

UNRWA has always been aware of the importance of helping the refugees to help themselves. Through its health education program it tries to teach them good health habits. Health education workers trained by a WHO specialist are now employed in camps to teach refugees the elements of hygiene and how to combat the spread of disease through proper health habits.

Malaria, which took a heavy toll of the refugees who first settled in the Jordan Valley, is being eradicated. An anti-malaria campaign involving the drainage of swamps and the use of DDT spraying was started by UNRWA four years ago in co-operation with WHO and the host governments. It has caused the incidence of this disease to drop from 18.5% of the total number of clinic attendances of sick refugees in East Jordan in 1953 to 0.66% in December 1957. Today each case of malaria is looked upon as a source of potential epidemic spread of the disease and receives as much attention as would be given to a case of smallpox.

To protect the refugees from contagious diseases the Agency regularly carries out large-scale preventive inoculation campaigns. Last year 254,000 refugees were inoculated against typhoid, 497,000 against smallpox, 51,000 against diphtheria and 32,000 against whooping cough.

Supplementary feeding

In spite of the inadequate calorie content of the dry rations distributed by UNRWA, there is surprisingly little evidence of malnutrition among the refugees. This is largely due to UNRWA's supplementary feeding and milk program, which furnishes special dry rations for a monthly average of 27,000 pregnant and nursing women and for non-hospitalized tuberculosis patients; provides milk for 190,000 children, nursing mothers and sick persons daily; and serves daily 46,600 supplementary hot mid-day meals to children and sick persons on doctors' orders.

Menus are specially prepared by a nutritionist and are standardized in all supplementary feeding centres in the four host countries.

Hospitals and clinics

For sick refugees UNRWA maintains 92 clinics (in camps, towns and villages) which receive an average of six million visits a year, as well as 2000 beds in hospitals of its own or in private and government hospitals which it supports.

Particular attention is given to expectant and nursing mothers who come to special maternal health

Canad. M. A. J.
June 15, 1958, vol. 78

centres run by the Agency for advice and treatment. Last year 100,000 consultations were recorded. As soon as pregnancy is diagnosed, a serological test for syphilis is made and positive cases are treated with antibiotics. Advice on preparation for delivery is given. Future mothers are taught the elements of child care and hygiene, and a simple layette is given to each. A training program for dayas, the traditional local midwives, has been undertaken. Mothers are encouraged to bring their babies for a regular check-up until the baby reaches the age of two. As a result, a sharp drop in the infant mortality rate among refugees has been recorded during the past two years.

Continuation of health services necessary

It is mostly because of the strict vigilance of UNRWA's health services that the refugees and the host countries have been spared from epidemics during the past ten years. As Mr. Henry R. Labouisse, Director of UNRWA, warned the twelfth session of the United Nations General Assembly, "disease would become an immediate threat to the refugees if the Agency were forced to curtail its health services because of the lack of funds." The majority of the Palestinian Arab refugees live in unsatisfactory housing conditions; the rations which UNRWA can afford to give them represent the very minimum for subsistence. In these circumstances it is essential for UNRWA to maintain its vigilance over the refugees' health and to continue to receive from governments the contributions to enable it to do so.

MEDICAL MEETINGS

SECOND WORLD CONGRESS OF GYNÆCOLOGY AND OBSTETRICS

The preliminary program of the Second World Congress organized by the International Federation of Gynæcology and Obstetrics, and due to take place in Montreal from June 22 to 28, is now available. The president of the Organizing Committee is Professor Léon Gérin-Lajoie and the vice-president Professor George B. Maughan. The committee has arranged a program consisting of main lectures (of which eight will take place on the mornings of Monday, Tuesday, Thursday and Friday), round table conferences on four afternoons (diagnosis of cervical carcinoma, toxæmias of pregnancy, genital tuberculosis, anæmia of pregnancy, limits of pelvic surgery in cervical cancer, psycho-prophylaxis for labour, psychosomatic medicine and ovarian function, and contraction of gravid uterus), and free communications in obstetrics and gynæcology, of which there are a great number. In addition films will be shown at the opening and closing of each day. The official opening is timed for Sunday evening, June 22, at 8.15; and there is a social program including a banquet and floor show on Wednesday evening, film shows on Monday and Thursday evening, and a theatrical entertainment on Tuesday evening. The City of Montreal is giving a reception at the Mount Royal Chalet on Monday evening, and the program ends with an evening visit to the St. Lawrence Seaway project.

Association Notes

THE CANADIAN MEDICAL RETIREMENT SAVINGS PLAN

This report covers C.M.R.S.P. activities during the quarter-year ending May 31, 1958. Moneys which participants have deposited in their special Bank of Montreal savings accounts on or before May 9, 1958, have been transferred to the Plan.

Contributions during this quarter totalled $217,175.38: $84,087.16 to the Insured Fund and $133,088.22 to the Common Stock Fund. Total contributions to date total $2,141,707: 38.4% to the Insured Annuity Fund and 61.6% to the Common Stock Fund.

Enrolment

As of December 31, 1957, 1,757 had registered their applications. Since that date we have enrolled a net increase of 36 participants. We anticipate that this number will increase measurably as the year progresses.

Annual Meeting Arrangements

We have arranged a special C.M.R.S.P. exhibit at The Association's Annual Meeting in Halifax. Officials of The National Life Assurance Company, The Royal Trust Company and the Bank of Montreal will be in attendance to provide information on the provisions of the Plan and to answer questions on details of its operation. The booth will be centrally located in the Lounge on the Mezzanine Floor of the Nova Scotian Hotel opposite the entrance to the Ballroom.

Notice to Non-Participants

To obtain more information about C.M.R.S.P., please write to The Association office at 150 St. George Street, Toronto. Brochures and other informative literature is available on request. The basic outline of C.M.R.S.P. is simple and extremely flexible, and participation will enable you to obtain tax relief now on savings which you invest to provide retirement income.

The Common Stock Fund

On May 31, the nucleus and corresponding members of the Trusteeship Committee met with officials of The Royal Trust Company to discuss investment decisions. You will note that, because of our dollar-averaging policy, a substantial amount of money is not as yet invested in common stocks. Decisions were reached as to policy in the investment of these funds during the next three months.

Unit Value

Even though moneys were not fully invested in common stocks, appreciation, dividends and interest resulted in an increase in the value of each common stock unit to $10.40 as of May 31, 1958.

CANADIAN MEDICAL RETIREMENT SAVINGS PLAN
COMMON STOCK FUND

Holdings Valued at Closing Prices, May 31, 1958

No. of Shares	*Description*	*May 31, 1958 Value*
1,150	Bank of Montreal	$50,600.00
450	Bank of Nova Scotia	26,325.00
800	Canadian Bank of Commerce	37,600.00
850	Royal Bank of Canada	52,381.25
575	Toronto-Dominion Bank	25,012.50
450	Distillers Corp.—Seagrams	12,825.00
450	Hiram Walker Gooderham & Worts	12,881.25
575	Molson's Brewery Class "A"	20,340.62
625	Canadian Breweries Ltd.	18,906.25
425	Building Products Ltd.	16,734.37
525	Canada Cement	16,275.00
575	Canadian Industries Ltd.	9,487.50
500	Simpsons Ltd.	10,187.50
700	Zellers Ltd.	21,000.00
100	Aluminium Ltd.	2,587.50
375	Moore Corp. Ltd.	26,250.00
425	Page Hersey Tubes	12,218.75
175	Dominion Glass	12,600.00
925	Consolidated Paper	30,293.75
400	Great Lakes Paper	11,450.00
525	Powell River Co.	15,618.75
475	St. Lawrence Corp.	6,115.62
450	Interprovincial Pipe Lines	20,137.50
250	Calgary Power	17,500.00
550	Gatineau Power	19,112.50
700	Shawinigan Water & Power	17,850.00
450	B.C. Power	17,381.25
850	Bell Telephone Co.	34,637.50
100	Union Gas Co. of Canada	8,150.00
450	Confederation Life	70,987.50
300	Manufacturers Life	73,650.00
50	E. I. Du Pont de Nemours	8,583.40
300	General Electric	17,275.22
150	Owens Illinois Glass	9,902.53
400	Standard Oil of New Jersey	20,576.06
	Cash	67.16
	Cash Equivalent (Royal Trust Guaranteed Receipts)	430,500.00
	Dividends declared but unpaid on stocks selling ex-dividend	2,322.94
		1,216,324.17
	Less: Administration Expense Allowance 1/8% quarterly	1,520.40
	Net Value of Fund	$1,214,803.77

On the basis of 116,761.383 outstanding units, the unit value is $10.40. Contributions made to the common stock fund during the three months prior to May 9 will purchase units at this rate.

Insured Annuity Fund

Some members have requested that figures for retirement at age 70 be shown. Table I, prepared by The National Life Assurance Company, illustrates the amount of monthly life annuity, guaranteed 120 months, which would be purchased by $100 monthly contributions accumulated at the guaranteed rate of 3.5% per annum.

TABLE I.

Entry Age	*Age at Retirement*	*Males*	*Females*
50	70	$242.28	$218.84
51	70	225.81	203.96
52	70	209.90	189.58
53	70	194.52	175.70
54	70	179.67	162.28
55	70	165.31	149.31
56	70	151.45	136.79
57	70	138.05	124.69
58	70	125.10	112.99
59	70	112.59	101.70
60	70	100.51	90.78
61	70	88.83	80.23
62	70	77.55	70.04
63	70	66.65	60.20
64	70	56.12	50.69
65	70	45.94	41.50
66	70	36.11	32.62
67	70	26.61	24.04
68	70	17.43	15.75
69	70	8.57	7.74

Table II shows the effect of accumulating contributions at 4.5% per annum. The amounts shown in this table of course are not guaranteed, as the maintenance of interest rates above the guaranteed level of 3.5% is dependent upon future insurance company interest earnings.

TABLE II.

Entry Age	*Retirement Age*	*Males*	*Females*
50	70	$269.77	$243.66
51	70	249.92	225.73
52	70	230.93	208.58
53	70	212.76	192.17
54	70	195.37	176.46
55	70	178.72	161.43
56	70	162.80	147.04
57	70	147.56	133.28
58	70	132.99	120.12
59	70	119.02	107.50
60	70	105.67	95.44
61	70	92.89	83.90
62	70	80.66	72.85
63	70	68.96	62.28
64	70	57.76	52.17
65	70	47.04	42.49
66	70	36.79	33.23
67	70	26.98	24.36
68	70	17.59	15.88
69	70	8.60	7.77

CANADIAN JOURNAL OF SURGERY

The July issue of the *Canadian Journal of Surgery* will include an index to the contents of all four numbers of the first issue of the journal (October 1957, January 1958, April 1958 and July 1958). Copies of all four issues of Vol. I may be obtained by writing to: The Canadian Journal of Surgery, 150 St. George Street, Toronto 5, Ont. Subscription is $10.00 for four issues.

Canad. M. A. J.
June 15, 1958, vol. 78

GENERAL HOSPITALS IN CANADA APPROVED BY THE CANADIAN MEDICAL ASSOCIATION FOR JUNIOR (1ST YEAR) INTERN TRAINING

Name of hospital	*Location*	*Beds (excluding bassinets)*	*Teaching beds*						*University affiliation***	*Number of junior interns accepted*	*Monthly salary*
			Public ward beds					*Private and semi-private*			
			Medicine	*Surgery*	*Obstetrics*	*Pædiatrics*	*Other*				
British Columbia											
Royal Columbian Hospital	New Westminster	434	136	138	34	48	12	66	no	12	$125
Trail-Tadanac Hospital	Trail	155	32	32	8	25	—	58	no	4	100
St. Paul's Hospital	Vancouver	551	24	25	6	20	—	—	U.B.C.	20	175
Vancouver General Hospital	Vancouver	1,282	92	243	54	154	68	92	U.B.C.	54	140
Royal Jubilee Hospital	Victoria	451	56	53	26	41	97	80	no	8	175
St. Joseph's Hospital	Victoria	442	126	104	34	71	—	107	no	9	175
Alberta											
Calgary General Hospital*	Calgary	743	146	220	59	84	39	195	no	16	100
Holy Cross Hospital	Calgary	336	50	79	32	50	—	125	no	12	100
Edmonton General Hospital	Edmonton	371	96	83	26	51	—	115	U.A.	10	100
Misericordia Hospital	Edmonton	342	54	60	34	50	2	142	U.A.	8	100
Royal Alexandra Hospital	Edmonton	755	127	45	92	74	143	131	U.A.	23	100
University of Alberta Hospital	Edmonton	1,078	388	323	32	139	—	196	U.A.	40	100
St. Michael's General Hospital	Lethbridge	181	27	19	18	28	—	89	U.A.	4	130
Saskatchewan											
Moose Jaw Union Hospital	Moose Jaw	244	39	39	7	19	44	96	no	5	150
Regina General Hospital	Regina	740	143	229	26	135	81	126	U.S.	25	150
Regina Grey Nuns' Hospital	Regina	471	114	156	27	50	16	108	no	20	200
St. Paul's Hospital	Saskatoon	277	66	68	16	33	26	68	U,S.	7	150
Saskatoon City Hospital	Saskatoon	350	95	101	15	32	53	54	U.S.	12	180 + bonus
University Hospital	Saskatoon	530	138	142	78	69	103	—	U.S.	16	100
Manitoba											
St. Boniface General Hospital*	St. Boniface	640	127	110	26	77	—	300	U.M.	28	$ 75
Grace Hospital	Winnipeg	221	16	19	21	6	—	159	U.M.	6	175
Misericordia Hospital	Winnipeg	512	78 combined		40	26	—	368	no	10	150
Winnipeg General Hospital*	Winnipeg	712	150	80	12	26	—	396	U.M.	32	25
Ontario											
McKellar General Hospital	Fort William	443	116	48	8	25	—	246	no	12	150
Hamilton General Hospital	Hamilton	1,184	52	52	19	33	160	868	no	26	125
St. Joseph's Hospital	Hamilton	457	44	53	28	54	—	278	no	16	150
Hôtel-Dieu Hospital	Kingston	288	59	23	15	15	—	176	Q.U.	15	140
Kingston General Hospital	Kingston	458	101	97	14	60	—	186	Q.U.	16	100
Kitchener-Waterloo Hospital	Kitchener	426	38	34	24	58	110	162	no	9	200
St. Joseph's Hospital	London	500	85	80	18	52	20	—	W.O.	17	125
Victoria Hospital	London	800	75	75	20	50	40	530	W.O.	28	100
Ottawa Civic Hospital	Ottawa	890	76	123	45	27	10	609	Q.U.	20	100
Ottawa General Hospital	Ottawa	622	52	36	24	60	68	382	U.O.	12	150 + bonus
General Hospital of Port Arthur	Port Arthur	287	61	44	28	41	22	91	no	4	200
St. Joseph's General Hospital	Port Arthur	198	44	27	7	40	—	80	no	2	150
St. Catharines General Hospital	St. Catharines	360	55	60	11	49	60	125	no	6	250
St. Joseph's Hospital	Sarnia	178	24	20	8	21	—	105	no	4	150
Sarnia General Hospital	Sarnia	247	35	29	8	46	10	119	no	6	215
Sudbury General Hospital	Sudbury	294	20	36	18	60	34	115	no	4	175
New Mount Sinai Hospital	Toronto	337	36	36	20	10	18	217	no	20	100
St. Joseph's Hospital	Toronto	519	91	102	32	58	31	205	no	20	125
St. Michael's Hospital*	Toronto	830	168	184	30	—	56	392	U.T.	32	50
Toronto East General and Orthopædic Hospital	Toronto	420	53	34	40	15	64	214	no	23	83
Toronto General Hospital*	Toronto	1,393	316	351	74	—	93	46	U.T.	42	50
Toronto Western Hospital*	Toronto	639	110	85	29	14	95	55	U.T.	30	75
Women's College Hospital	Toronto	279	49	21	49	4	26	130	U.T.	8	75
Grace Hospital	Windsor	219	23	20	21	36	—	119	no	4	300
Hôtel-Dieu of St. Joseph	Windsor	349	52	93	30	56	8	110	no	8	300
Metropolitan General Hospital	Windsor	313	54	38	4	25	28	134	no	4	300
Quebec											
Hôtel-Dieu Saint-Vallier	Chicoutimi	799	97	132	9	105	151	305	U.L.	22	25
Hôpital St-Luc	Montreal	415	94	167	15	5	—	134	U.L. and M.	15-20	90
Hôtel-Dieu de Montréal*	Montreal	751	147	124	—	—	—	480	M.	22	40
Jewish General Hospital	Montreal	314	48	45	27	21	44	129	McG. U.	16	60
Maisonneuve Hospital	Montreal	514	39	49	5	55	24	342	M.	19	40
Montreal General Hospital*	Montreal	721	102	102	—	—	154	322	McG. U.	48	40
Notre-Dame Hospital	Montreal	615	70	60	10	50	115	310	M.	30	40
Queen Elizabeth Hospital****	Montreal	124	14	26	8	—	—	76	McG. U.	9	100
Royal Victoria Hospital	Montreal	913	60	90	54	37	100	381	McG. U.	24-28	40
Reddy Memorial Hospital***	Montreal (Westmount)	140	10	18	14	3	5	90	McG. U.	7	100
St. Mary's Hospital	Montreal	236	40	39	13	12	—	132	no	16	100
Hôpital de l'Enfant-Jésus	Quebec	502	—	—	—	—	—	—	U.L.	20	Nil
Hôpital du Saint-Sacrement*	Quebec	302	48	34	—	15	35	170	U.L.	18	Nil
Hôtel-Dieu de Québec	Quebec	332	90	90	36	38	78	—	U.L.	15	Nil
Jeffery Hale's Hospital	Quebec	150	12	12	4	12	—	110	U.L.	4	100
Hôtel-Dieu de Sherbrooke	Sherbrooke	296	50	50	22	20	—	154	no	8	50
Hôpital Général de Verdun	Verdun	420	60	44	8	42	—	119	M.	7	40
New Brunswick											
Victoria Public Hospital	Fredericton	169	47 combined		7	26	13	76	D.U.	3	75
Moncton Hospital	Moncton	210	16	16	8	42	—	128	D.U.	6	75
Saint John General Hospital	Saint John	403	47	82	23	50	80	121	D.U.	10	75
Nova Scotia											
Halifax Infirmary*	Halifax	228	44 combined		21	—	—	163	D.U.	6	50
Victoria General Hospital*	Halifax	549	122	215	—	—	—	212	D.U.	30	75
Newfoundland											
St. John's General Hospital*	St. John's	456	56	123	—	35	139	50	D.U.	15	208

*Hospitals having arrangements with other hospitals for part of intern training.

Parent hospitals	*Hospitals supplementing intern training*
Calgary General Hospital, Calgary, Alta.	Salvation Army Grace Maternity Hospital, Calgary (Antenatal Clinics)
St. Boniface General Hospital, St. Boniface, Man.	Children's Hospital, Winnipeg (Pædiatrics) D.V.A., Winnipeg (Medicine)
Winnipeg General Hospital, Winnipeg, Man.	Children's Hospital, Winnipeg (Pædiatrics)
St. Michael's Hospital, Toronto, Ontario	Hospital for Sick Children, Toronto (Pædiatrics)
Toronto General Hospital, Toronto, Ontario	Hospital for Sick Children, Toronto (Pædiatrics)
Toronto Western Hospital, Toronto, Ontario	Hospital for Sick Children, Toronto (Pædiatrics)
Hôtel-Dieu de Montréal, Montreal, Quebec	Hôpital Ste-Justine, Montreal (Obstetrics and Pædiatrics)
Montreal General Hospital, Montreal, Quebec	Catherine Booth Mothers' Hospital, Montreal (Obstetrics) Montreal Children's Hospital, Montreal (Pædiatrics) Charlotte Memorial Hospital, Charlotte, North Carolina (Medicine, Surgery, Obstetrics and Pædiatrics)
Hôpital du Saint-Sacrement, Quebec, Quebec	Hôpital de la Miséricorde, Quebec (Obstetrics)
Halifax Infirmary, Halifax, N.S.	Children's Hospital, Halifax (Pædiatrics)
Victoria General Hospital, Halifax, N.S.	Halifax Children's Hospital, Halifax (Pædiatrics) Grace Maternity Hospital, Halifax (Obstetrics)
St. John's General Hospital, St. John's, Newfoundland	Grace Hospital, St. John's (Obstetrics)

***University abbreviations used in list of approved hospitals.*

U.B.C.—University of British Columbia
U.A. —University of Alberta
U.S. —University of Saskatchewan
U.M. —University of Manitoba
Q.U. —Queen's University
W.O. —University of Western Ontario
U.O. —University of Ottawa
U.T. —University of Toronto
U.L. —Laval University
M. —University of Montreal
McG.U.—McGill University
D.U. —Dalhousie University

***Credit for additional beds given for Home Care Service.
****Credit for additional beds at Montreal Children's Hospital.

LETTERS TO THE EDITOR

STIMULATING ACTION OF X-RAYS

To the Editor:

The discussion on radiation hazards is still very much to the fore in the medical and general press. Since x-rays are one of the most frequently used artificial ionizing radiations the attack is primarily directed against them. There are two sides to this problem. One is indisputable: The indiscriminate use of x-rays and ample doses of radiation provokes local or general changes in living matter incompatible with living processes. From the beginning of the x-ray era radiologists have combated overdosage of x-rays. Industry supplies us with effective protective measures which restrict the direct danger of x-rays to a negligible minimum. The other side of the problem is the possible damage caused by comparatively small doses of x-rays. This question is closely connected with the mode of action of x-rays on living matter. The majority of biologists assume that this action is an "all or none" event. In other words, there is a threshold on one side of which (subliminal doses) there is no action at all, while on the other side the action is always injurious to structure and function. The link between these two actions constitutes the cumulation of x-ray effect. Because of this, even small doses of x-rays, singly harmless, may in the long run produce an irreversible injury through their cumulation. Since the cell may recover from a single x-ray attack if this is not destructive enough, it is necessary to find out this reversible "tolerance dose". American and British Committees on Radiation agreed that such a dose cannot be greater than 0.3 r per week for anyone in constant contact with radiation. For a single diagnostic procedure the recommended maximum is around 30 r; for x-ray therapy the limit is determined by therapeutic indications.

Another side of the problem is genetic. According to Muller and his followers,[4] x-rays destroy genes and consequently produce unfavourable mutations in future generations. Such mutations have been demonstrated by Muller for *Drosophilia melanogaster* (fruit fly) with a short life span; and for mice by Russel and others.[4] In human beings, according to Muller,[5] 750 to 3000 years should pass before the recessive abnormality caused by x-rays would manifest its serious nature. No wonder that some geneticists (Fritz-Niggli[3]) consider that "there is insufficient evidence for accurate estimate of the danger to human hereditary material from radiation".

After these preliminary remarks, we wish to refer to the main subject of this letter—the action of very small doses of x-rays on living matter. We have in mind doses which are subliminal (see above) even after cumulation. However, can we be quite certain that these smallest doses of x-rays do not produce disturbances in cells which in some way or other may influence the living process? If the function of the cell is enhanced by x-ray action, we may call this "stimulation" and the action of x-rays "stimulant". We will not analyze in detail the cause of the stimulant effect. It may possibly be due to the direct influence of x-rays or to the influence of some product of cell activity liberated by x-ray action. We are even prepared to go so far as to assume the possibility of stimulant action caused by products of cell necrosis of those cells which became victims of a direct hit with an x-ray quantum (photons). In living organisms there

Canad. M. A. J.
June 15, 1958, vol. 78

is always an exchange between living and dead cells. Cells may die for various reasons, including x-ray action. The resulting products of cell disintegration act, according to many authors, as some kind of "hormone" (Caspari called them "necrohormones") stimulating the activity of living cells. In health the exchange between living and dead cells is in balance; in disease the equilibrium is broken. Whatever the reason—direct or indirect—the stimulant action if caused by x-rays may be called x-ray stimulation.

There is much literature on x-ray stimulation; some of it is debatable. Many observations, however, deserve very serious attention.

In 1952 Brunst[2] reported that he observed the development of a second tail in the axolotl (*Siredon mexicanum*) under the influence of small doses of x-rays (on the periphery of the irradiation field). In view of the comparatively low sensitivity of amphibia to x-rays, these results are very significant, and Brunst is right in his conclusion that "it seems clear that one can no longer ignore the phenomenon of roentgen stimulation". Brunst's paper has a large bibliography on the subject.

In 1953, Pape[6] reported that under the influence of small doses of x-rays (1-20 r) he observed a stimulant effect on hæmopoiesis, which might be exploited therapeutically. Some of his patients with leukæmia given a dose as small as 3.2 r per month in whole body irradiation could be kept alive for 4-6 years and even longer.

In the same year, Trautmann *et al.*[7] reported results of experiments with male rates. The whole body was irradiated with ¼ r daily for 80-100 days. Afterwards this irradiated group and a non-irradiated control group received massive doses (from 300 to 3000 r) in whole body irradiation. No control animal survived eight days after the massive dose; all animals of the first group survived and were sacrificed on the ninth day. Testes of the animals were chosen for histological studies as organs very sensitive to radiation. In the first group, only insignificant changes were observed. In the control group, complete destruction of spermatogonia was observed. The authors conclude that small doses of x-rays enhance the resistance of animals to radiation. These experiments are very significant because we are living in an atmosphere full of small doses of ionizing radiation (cosmic rays, earth and body radiation, etc.).

Just before World War II the author of this letter[1] had started a series of experiments with rabbits inoculated with Brown-Pearce cancer. Four groups of rabbits were studied. The first was irradiated with small doses of x-rays (5 r weekly) for 2-3 weeks and then inoculated with Brown-Pearce tumour. The second group was inoculated with tumour and then irradiated with the small doses mentioned above. The third group received massive doses (1000 r in several seances) and was then inoculated with tumour. The fourth group was inoculated without x-ray treatment. The whole body was irradiated in the natural position of the animals. On the twentieth day all surviving animals were sacrificed. No more than 30% of the animals of the third group survived. The most numerous failures of inoculation were observed in the first group. In both the first and the second groups, inoculated tumours developed very slowly and in some animals disintegrated, metastases being scanty or absent. The most malignant course was observed in the third group, practically no organ being free of metastases. In some animals, even the spleen was full of them. Unfortunately we were unable to repeat these experiments on a larger scale and they remained unpublished. We might explain the positive results in the first two groups on the stimulant action of small doses of x-rays on the reticulo-endothelial system (RES) which, in our opinion constitutes one of the factors in the resistance of living organisms to neoplasia, infection, etc. The depression of this system and the subsequent malignant course of the tumour disease were well demonstrated in the third group. The sensitivity of elements of the RES to x-rays is well known.

The above is sufficient for one to conclude that the problem of x-ray stimulation should be studied in all its details. It is possible that doses of x-rays might be decreased still more than those used by experimenters. It is necessary to find out which organs and which cells are especially sensitive to stimulation, in which conditions this stimulation is especially effective, etc.

The possibility of stimulating resistance to cancer with the smallest doses of x-rays, suggested by the experiments mentioned above, deserves special attention.

X-rays are a real benefactor to mankind. Many lives have been saved by well-timed x-ray diagnosis and therapy. This letter is to direct attention to the possibility of yet another beneficial action of x-rays, i.e. the stimulating action of small doses.

F. BOHATIRCHUK, M.D.

Associate Professor,
The University of Ottawa,
Ottawa, Ont.,
April 25, 1958.

REFERENCES

1. BOHATIRCHUK, F.: Unpublished.
2. BRUNST, V. V.: *Am. J. Roentgenol.*, **68**: 281, 1952.
3. FRITZ-NIGGLI, H.: *Fortschr. Geb. Röntgenstrahlen*, **87**: 427, 1957.
4. MULLER *et al.*: Advances in radiology. Proceedings of the Fifth International Conference in Stockholm, 1956. Edited by George Carl de Havesy, Carl Gunnar Forsberg and John D. Abbat. Oliver & Boyd, London and Edinburgh, 1957.
5. PINCUS, G.: *Science*, **93**: 438, 1941 (Abstract).
6. PAPE, R.: *Strahlentherapie*, **91**: 108, 1953.
7. TRAUTMANN, J., FREY, J. G. AND SCHAAF, J.: *Ibid.*, **91**: 602, 1953.

ABSTRACTS *from current literature*

MEDICINE

Inaccuracy of Wedge Pressure as an Index of Pulmonary Capillary Pressure.

J. P. MURPHY: *Circulation*, 17: 199, 1958.

Wedge and left atrial pressures were compared on 12 patients with congenital and acquired heart disease. In five patients the left atrial pressures were not elevated and the wedge pressures showed similar contours and corresponding values. In seven patients with elevated left atrial pressures the wedge pressures did not reflect these elevations with quantitative differences ranging from 9 to 33 mm. Hg. Two patients with clinical pulmonary œdema and mean left atrial pressures of 50 and 41 had mean wedge pressures of 20 and 16. Thus, in this study the wedge pressures paralleled the left atrial pressures when the latter were within normal ranges. The wedge pressures failed to reflect the left atrial pressures by significant values when the left atrial pressures were elevated.

S. J. SHANE

Cystic Cavities in Pulmonary Tuberculosis Treated with Isoniazid.

V. ALTMANN AND R. M. DIAZ: *Am. Rev. Tuberc.*, 77: 221, 1958.

The authors feel that thin-walled, regular defects with smooth outlines observable on roentgenograms may be healing or healed tuberculous cavities, but that their true nature cannot be reliably established by roentgenographic examination alone. The presence or absence of other lesions suggestive of tuberculosis, together with the information whether the sputum is positive or negative for tubercle bacilli, always influences opinions concerning these defects.

In any patient with a cystic defect in the lung, in which the sputum only occasionally contains tubercle bacilli, there is a possibility that the cysts might not be active tuberculous cavities and that the specimens of infectious sputum in such cases might be due only to active noncavitary lesions. These cysts, consequently, may become a source of much confusion and of erroneous interpretation. Conservative therapy for prolonged periods is probably advisable in most of these instances, especially in the absence of roentgenographic evidence of spread of disease. When the disappearance of tubercle bacilli from the sputum has been maintained for 12 months or longer, these cysts, in most cases, prove to be free of active tuberculosis.

Roentgenographic appearance, results of sputum examinations, and the possibility of other tuberculous lesions shown in the roentgenograms have to be considered together in order to arrive at practical conclusions regarding the possible true nature of these cysts. In the presence of sputum positive for *M. tuberculosis*, inactive cysts may be erroneously considered to be active tuberculous cavities, resulting in an improper choice of treatment. S. J. SHANE

Dangers of and Contraindications to Laparoscopy (Peritoneoscopy), Particularly Liver and Spleen Biopsy (*In German*).

F. J. ROSENBAUM: *Deutsche med. Wchnschr.*, 83: 222, 1958.

Personal experience with 800 peritoneoscopies is reported. The dangers of simple peritoneoscopy and that of biopsy of liver and spleen under direct vision is emphasized. In 11 examinations, serious incidents were encountered, five of them in extrahepatic biliary obstruction, four in cholangiography, and one each in cirrhosis of the liver and metastatic liver involvement. Four of these incidents resulted in death, and as one of these occurred in metastatic liver disease it was decided to avoid biopsy of metastases in future. In extrahepatic biliary obstruction two fatalities emphasize the danger of biopsy. Transhepatic cholangiography was performed in 25 cases and the high incidence of complications (4) suggests the use of this examination only when absolutely necessary. The author could not confirm the findings of Kalk, that the colour of the liver is diagnostic for the etiology of icterus. Thus a typical green liver was present in only 55% of his cases of biliary obstruction. In two cases of biliary obstruction not diagnosed ante mortem, the liver was brown. Needle biopsy of the spleen caused fatal hæmorrhage in a case of brucellosis which was undiagnosed. Indications for biopsy even under direct vision should be strictly circumscribed in order not to discredit peritoneoscopy, which is a valuable method of diagnosis. W. GROBIN

Bronchospirometry in Pulmonary Neoplasms (*In German*).

E. GYURECH-VAGO AND M. SCHERRER: *Schweiz. med. Wchnschr.*, 88: 227 and 261, 1958.

Bronchospirometry disclosed in 11 of 19 cases of lung tumour that oxygen uptake was reduced in the affected lung whilst vital capacity remained normal or nearly so. This is explained by the authors as indicating invasion or stenosis of major pulmonary vessels by the growth. Significantly, this discrepancy between vital capacity and oxygen uptake was not found in peripherally situated tumours. According to the authors, reduced oxygen uptake was associated with metastases and the prognosis was unfavourable. They suggest that cases in which reduced oxygen uptake is found be treated conservatively and not subjected to useless operation. W. GROBIN

The Hæmodynamic and Clinical Characteristics of Rheumatic Aortic Stenosis.

H. GOLDBERG *et al.*: *Dis. Chest*, 33: 201, 1958.

The physiologic and clinical characteristics of aortic stenosis are presented in 45 cases studied by combined heart catheterization, 39 of which came to surgery. A constant finding is the presence of a systolic pressure gradient at the aortic valve. The aortic valve flow is generally reduced, and the average valve area was calculated to be 0.5 sq. cm. (normal 3.0 sq. cm.). The clinical triad of dyspnœa, angina and syncope or some combination of these appears when the valve area is reduced below 1.0 sq. cm. The lack of correlation between the physiologic data and the severity of symptoms is discussed.

It would appear that once a patient with aortic stenosis develops dyspnœa, angina or syncope, or some combination of these, a physiologically significant degree of obstruction is present and the aortic valve area is less than 1 sq. cm., one-third of normal. That a critical aortic valve area exists was suggested by others. Once the valve orifice has been reduced to this critical size, the type and degree of symptoms may be variable. Electrocardiographic and radiologic evidence of left ventricular enlargement only confirms the physiologic significance of the lesion. This concept is confirmed also by the physiologic and clinical changes that follow surgery for this lesion. After aortic commissurotomy, Smith and associates found in 17 patients in this series that although the pressure gradient is only occasionally eliminated (in two cases) and physiologic obstruction is still present, the symptom triad of dyspnœa, angina and syncope is relieved in those cases where the calculated postoperative valve area has been brought above 1 sq. cm. S. J. SHANE

The Emphysema Response to Forced Straining.

H. MILLS AND A. A. KATTUS, JR.: *Circulation*, 17: 65, 1958.

In the majority of patients with pulmonary emphysema the forced straining of the Valsalva manœuvre leads to a unique circulatory response. This "emphysema response" has two characteristics: marked diminution in terminal straining pulse pressure, frequently to the point of obliteration, and considerable delay in the return of post-straining systolic pressure to the control level. The emphysema response appears to be an exaggeration of the normal response to the Valsalva manœuvre and is most marked in those patients with emphysema who have low cardiac output and small pulmonary blood volume. S. J. SHANE

Canad. M. A. J.
June 15, 1958, vol. 78

Pulmonic Valvular Stenosis Associated with Interatrial Septal Defects.

J. L. EHRENHAFT *et al.*: *Dis. Chest*, 33: 193, 1958.

Twelve cases of valvular pulmonic stenosis with either right-to-left or left-to-right interatrial shunts are reported. The direction and volume of the interatrial shunt is ultimately a function of the severity of the valvular pulmonic stenosis. Both defects were corrected in all of these patients by open cardiotomy, hypothermia being used in 11 and a pump-oxygenator in one. There were no deaths. Since the most common associated defect in patients with valvular pulmonic stenosis is an atrial septal defect, atrial exploration is indicated in all patients undergoing surgery for valvular pulmonic stenosis. The method used should permit correction of both defects at the same operation by open cardiotomy.

S. J. SHANE

Fungal Endocarditis: Review of the Literature and Report of Three Cases.

R. K. MERCHANT *et al.*: *Ann. Int. Med.*, 2: 242, 1958.

This is a review of 31 previously reported cases of fungal endocarditis; three additional cases (two due to *H. capsulatum* and one to *C. immitis*) are reported. The fungi implicated are candida, blastomyces, coccidioides, aspergillus, cryptococcus, histoplasma and mucor. Candida and histoplasma endocarditis are the most common, each comprising about a third of the 34 cases. In some cases endocarditis is not clinically evident, and occurs as an apparently minor manifestation of overwhelming generalized mycotic infection. However, the majority of the cases resemble subacute bacterial endocarditis, and in these cases endocarditis was an important manifestation of the mycotic disease.

Aside from cases where the diagnosis of fungal endocarditis is readily apparent, there are two clinical situations in which it should be seriously considered. One such is seen in the patient with known systemic fungal disease who has physical signs suggestive of endocarditis. Significant heart murmurs and evidence of major emboli are the most important physical findings because several other findings usually associated with endocarditis (fever, anæmia, splenomegaly, etc.) also occur commonly in systemic fungal disease without endocarditis.

The other clinical situation that should suggest the diagnosis of fungal endocarditis is seen in the patient with a clinical picture of subacute bacterial endocarditis whose routine blood cultures are sterile and who has no obvious evidence of mycotic infection. In such a case blood cultures for fungi should be obtained, and a careful search should be made for evidence of fungal infection elsewhere by culture of urine, bone marrow, and lymph nodes, and adequate histologic examination of tissue obtained by biopsy. If evidence of systemic mycotic infection is found, it may be an important clue to the nature of the endocardial process.

The authors consider that awareness of endocarditis as a manifestation of fungal disease, and the use of cultural and histologic techniques appropriate for the demonstration of fungi, will allow the diagnosis of fungal endocarditis to be made more frequently during life.

S. J. SHANE

Prolonged Observations of Patients with Cor Pulmonale and Bullous Emphysema after Surgical Resection.

M. J. FITZPATRICK *et al.*: *Am. Rev. Tuberc.*, 77: 375, 1958.

Pulmonary emphysema, a predominantly degenerative pulmonary disease of aging males, is most frequently associated with chronic bronchitis. Its course is usually spread over many years with a gradual and progressive reduction of pulmonary reserve. The resultant abnormal lung volumes, the obstructive pattern of air flow, the increased work of breathing, and the abnormal ventilation-perfusion relationships are frequently associated with a gradual anatomic reduction in capacity of the normal voluminous capillary bed and, in some patients, with the development of fixed pulmonary hypertension with secondary cardiovascular and hæmatologic changes. These lead to a readjustment of the right heart to an increased work load to maintain normal flow through this restricted vascular bed. Intercurrent bronchial infections with associated augmentation of hypoxæmia further accentuate these abnormalities and contribute ultimately to cardiac hypertrophy with dilation and failure of the right heart.

Seven "poor risk" patients with chronic pulmonary emphysema, cor pulmonale, and large bullæ had surgical ablation of the bullæ. Six survivors were followed for a minimum of one year after operation. During this period changes in lung function, cardiovascular dynamics, and the hæmatologic system were observed.

In the majority of the patients, no significant improvement was noted in ventilation following operation. This is compatible with the protracted course and the diffuse nature of emphysema. Some objective benefits from operative intervention were observed in the more recently acquired cardiovascular and hæmatologic changes. In those patients whose bronchitis and emphysema showed further progression after operation, the benefits of the operation proved to be of short duration, with a gradual return to preoperative abnormalities during the following year. In other patients whose basic disease failed to progress as rapidly after operation, reversion of the cardiovascular and hæmatologic abnormalities to more normal levels was of longer duration. In one patient with chronic bronchitis and an epithelized bronchogenic cyst, no changes in cardiopulmonary or hæmatologic values were observed after excision. Symptomatic improvement correlated best with a mechanical increase in ventilation.

S. J. SHANE

Bronchodilators and Corticosteroids in the Treatment of Obstructive Pulmonary Emphysema.

W. FRANKLIN *et al.*: *New England J. Med.*, 258: 774, 1958.

Bronchodilator drugs and corticosteroids are of value in the treatment of obstructive pulmonary emphysema. Fifty-eight patients were carefully studied while being treated with bronchodilators and in half the group corticosteroids were also employed. Combined treatment with both agents resulted in a mean increase in vital capacity and first-second volume of almost 50% of the pretreatment value. The improved respiratory exchange often produced subjective improvement of greater proportion than indicated by objective findings.

Peptic ulcer is commonly present in patients with emphysema (13 of this group of 58), as is congestive heart failure (six patients). In only one case was there any evidence of deleterious effect upon the secondary condition from the employment of corticosteroids.

Bronchodilator drugs and the corticosteroids would appear to be of definite value in the therapy of emphysema.

NORMAN S. SKINNER

Artificial Pneumothorax as an Aid to Chemotherapy in the Treatment of Pulmonary Tuberculosis.

A. F. FOSTER-CARTER: *Dis. Chest.*, 33: 382, 1958.

Analysis of 174 patients, treated with unilateral pneumothorax and antimicrobial therapy during the past six years, suggests that most of the former disadvantages of artificial pneumothorax have now disappeared; but it is also shown that more effective chemotherapy is reducing the need of artificial pneumothorax, in common with other forms of treatment.

Artificial pneumothorax still has a small but important role in treatment. Reasons are given why it is preferable to other types of therapy in certain situations. It is suggested that the practice of intrapleural pneumolysis is no longer necessary and should now be discontinued. The duration of artificial pneumothorax can now be greatly reduced and the use of this treatment for short periods may prove to be valuable in promoting early cavity closure.

S. J. SHANE

SURGERY

Visual Repair of Congenital Aortic Stenosis during Hypothermia.

H. SWAN *et al.*: *J. Thoracic Surg.*, 35: 139, 1958.

The differential diagnosis between aortic-valve and subvalvular obstruction remains most difficult, if not at times impossible. In the past it has not been considered that the clinical evaluation of the patient offers any findings that will allow this differential diagnosis. Some authors have held that the recorded arterial pulse tracing offers distinctive features, but most observers are not in agreement with this statement. At the present time, it is the opinion of most that ancillary investigations, such as left heart catheterization and angiocardiography, likewise will not enable this differential diagnosis to be established with any degree of certainty.

The factors that are discussed in this paper are certainly not believed to be definitive in establishing anatomic diagnosis; however, the authors have found them helpful. Thus, the finding of the harsh, systolic murmur of maximum intensity in the third interspace, just to the left of the sternum or beneath the sternum, is considered to point towards the obstruction's being at the subaortic proximal portion of the aorta, that is, within the area of the sinuses of Valsalva, and also points towards a subaortic stenosis. When both of these points are definitely noted, the diagnosis of subaortic stenosis is made. In this series, the diagnosis of subvalvular obstruction was made in four patients, and was correct in three.

As a result of their surgical experience, the writers are of the opinion that open operation upon the congential aortic-valve and subvalvular stenosis is technically feasible under hypothermia with circulatory occlusion. Moreover, the pathology of the congential obstructions is such that an excellent result can be achieved. The operation has definite risks and should be applied, at the present time, only in selected patients. The underlying theory that the pathology of congenital valvular obstruction will allow incision in the commissures with maintenance of competence of the cusps has been shown to be generally true. However, in this series, aortic regurgitation has occurred sufficiently often to suggest that the operator should err on the side of conservative relief of stenosis in order to prevent the undesirable occurrence of regurgitation as a serious complication of surgery. Incisions into commissures, therefore, should be placed only in those commissures and only for such a distance that the operator feels quite confident that both adjacent cusps will remain competent. Most consistent results in the long run, therefore, will be achieved by the subvalvular type of obstruction, since in these patients the risk of creating regurgitation does not exist and if care is taken not to injure the aortic leaflet of the mitral valve, relief of obstruction should be quite adequate.

Because of the precision required in the actual operative manœuvres for the correction of congenital aortic stenosis, it is the firm conviction of the authors that open direct-vision technique is an essential component of the surgical therapy of this lesion.

S. J. SHANE

A Rational Approach to the Surgical Treatment of Duodenal Ileus.

J. H. LOUW, B. SENDER AND B. SHANDLING: *South African J. Lab. & Clin. Med.*, 3: 249, 1957.

Many theories have been put forward to explain duodenal obstruction in the newborn, sometimes only becoming evident in adolescent or adult life. The concept of arteriomesenteric ileus and congenital megaduodenum is attacked as a result of a study of 41 cases of anomalous intestinal obstruction. That duodenal compression is often found to be the result of malrotation is shown by the presence of some degree of duodenal ileus in 31 of these patients.

Treatment of duodenal obstruction by surgical means is the only satisfactory one. The mobilization of the right colon and duodenum with division of the ligament of Treitz as described by Ladd gives results superior to duodenojejunostomy. The results of the Ladd procedure were excellent in 25 cases which included children and adults as well as infants, and it corrected the associated steatorrhœa as well as the duodenal obstruction.

BURNS PLEWES

Carcinoma of the Lung Treated by Lobectomy: The Problem of Local Recurrence.

R. H. HOLLAND: *J. Thoracic Surg.*, 35: 274, 1958.

Two proved cases and two probable cases of recurrent squamous-cell carcinoma of the bronchial stump occurred in a series of 21 lobectomies for carcinoma of the lung. The writers feel that the exact incidence of this condition is probably underestimated because of the difficulty in following up all patients individually. The symptoms of a persistent cough, hæmoptysis and inanition are considered evidence of bronchial stump recurrence until proved otherwise.

The prognosis of a local recurrence is poor. Radiation therapy has been of little or no help, and further

Canad. M. A. J.
June 15, 1958, vol. 78

surgery is considered meddlesome. It is felt that the underlying pathology and pulmonary functional status of the patient should determine the extent of resection rather than enthusiasm for a particular operative procedure or the unsuppressed desire to preserve all normal lung tissue.

The authors consider that, for that most part, squamous-cell carcinomas should be treated by pneumonectomy. Lobectomy and bilobectomy should be reserved for some peripherally placed adenocarcinomas and large-cell undifferentiated carcinomas if the hilar lymph nodes are negative for carcinoma on frozen section.

S. J. SHANE

Pulmonic Stenosis with Intact Ventricular Septum: Treatment Utilizing Extracorporeal Circulation.

D. C. MCGOON AND J. W. KIRKLIN: *Circulation*, 17: 180, 1958.

Pulmonic stenosis with presumably intact ventricular septum is frequently a complex abnormality, for the stenosis may be valvular or infundibular and may be associated with an atrial septal defect or even with a small ventricular septal defect. The feasibility of complete correction of these several possible associated cardiac abnormalities, by means of extracorporeal circulation and open cardiotomy, is exemplified by the reported series of 10 cases without operative mortality, in 9 of which an excellent result was obtained. One patient died three months after operation.

S. J. SHANE

The Dependency of Thyroid Cancer.

C. G. THOMAS: *Ann. Surg.*, 146: 879, 1957.

Like carcinoma of the breast and carcinoma of the prostate, some other tumours of the endocrine system may exhibit a relationship to their trophic hormone. Thus carcinoma of the thyroid gland may be not strictly autonomous in its biologic activity but influenced by an environmental factor. Both experimentally and in clinical cases, the suppression of thyrotropic hormone by the administration of excessive amounts of desiccated thyroid or other thyroid hormones has been beneficial. Both the primary tumour and metastases have been inhibited, sometimes for many years, by the daily administration of exogenous thyroid. Which cancers can be thus controlled is not predicted by the histologic appearance.

Total thyroidectomy is still the best treatment of the primary carcinoma, and thyroid hormone should be given both to prevent hypothyroidism and to treat any remaining tumour. Clinical hyperthyroidism may or may not occur with large doses of thyroid hormone, for there is great individual variation.

BURNS PLEWES

Further Studies in the Pathogenesis of the Postgastrectomy Syndrome.

G. H. PEDDIE, G. L. JORDAN, JR., AND M. E. DE BAKEY: *Ann. Surg.*, 146: 892, 1957.

In a series of patients who had undergone subtotal gastrectomy, most of whom had the dumping syndrome (sweating, nausea, weakness, pallor and tachycardia, and perhaps diarrhœa) serial determinations were made of plasma volume and potassium levels and electrocardiographic recordings. Out of 16 symptomatic patients, 14 showed a decrease in postprandial plasma volume averaging 420 ml. A postprandial fall in serum potassium was recorded in every patient studied, the average fall being greater in patients with symptoms. Electrocardiographic alterations were also more marked in those with the dumping syndrome.

It is concluded that the rapid passage of fluid from the blood stream into the intestine is an important feature of the dumping syndrome but that identical symptoms may be exhibited without this phenomenon. Alterations in the concentration of serum potassium may be important in the occasional case.

BURNS PLEWES

Healing of Vascular Grafts.

A. I. S. MACPHERSON AND R. B. DUTHIE: *J. Roy. Coll. Surgeons Edinburgh*, 3: 98, 1957.

A histologic, histochemical and autoradiographic study was carried out on grafts to replace the abdominal aorta in dogs. The living autograft survived and was indistinguishable from the host vessel for periods up to 13 months after implantation. Homografts preserved by freezing and drying, though not viable, were accepted by the host and did not undergo phagocytosis or replacement during 26 months, for elastic and collagen fibres persisted. The healing of homografts by ground substance and mesenchymal cells leads to the formation of a new endothelium and intima from the connective tissue cells of the host. Dense fibroplasia gave rise to longitudinally orientated fibres of connective tissue along the external surface of the homograft and added mechanical strength.

The appearance of foci of hyperplasia and metaplasia in the perivascular tissues about the graft at 26 months may be potential areas for the formation of calcific plaques and mucinous degenerations.

BURNS PLEWES

THERAPEUTICS

Persistence of Tubercle Bacilli in the Organs of Guinea-Pigs under Chemotherapy.

L. F. BOJALIL, R. PEREZ-TAMAYO AND F. BASTARRACHEA: *Am. Rev. Tuberc.*, 77: 473, 1958.

Guinea-pigs infected with an appropriate dose of tubercle bacilli and treated since the day of infection with isoniazid and streptomycin for 15 and 30 days showed fewer lesions the longer the treatment was continued. A similar group of animals treated for 60 days failed to show any morphologic evidence of tuberculosis at the end of treatment. However, 240 days after discontinuation of treatment, lesions which were limited to the lymph nodes appeared. Different guinea-pigs subinoculated with one of several organs of animals treated for 15 and 30 days developed tuberculosis. When subinoculation was carried out in the same manner with macerates of organs of animals treated for 60 days, no evidence of tuberculosis was present despite the fact that the subinoculated guinea-pigs became tuberculin-positive. This indicates that viable tubercle bacilli remained in the tissues of guinea-pigs after 15-30 days of antimicrobial therapy.

S. J. SHANE

PATHOLOGY AND EXPERIMENTAL MEDICINE

Immune Electrophoresis *(In German).*

C. WUNDERLY: *Deutsche med. Wchnschr.*, 83: 407, 1958.

Immune electrophoresis, a further refinement in the separation of fractions of serum proteins, is a com-

bination of electrophoresis with serologic precipitation in an agar gel. The method is described and the extensive literature quoted. The findings in cases of doubling of the albumin fraction, and in hypo- and a-gammaglobulinæmia are presented and compared with the older methods of electrophoresis. The results in cases of macroglobulinæmia are compared with the Ouchterlony plate test and with those using the ultracentrifuge. With further refinement of this method by the use of immune serum of high titre, it should be possible to discover new components of serum proteins which until now have been lumped under the name of "paraproteins". Illustrations and diagrams accompany this paper. W. GROBIN

Tissue Culture Studies on Resistance in Tuberculosis. I. Normal Guinea-Pig Monocytes with Tubercle Bacilli of Different Virulence.

M. BERTHRONG AND M. A. HAMILTON: *Am. Rev. Tuberc.*, 77: 436, 1958.

In this study, tissue culture experiments were carried out, employing normal guinea-pig monocytes infected with various strains of tubercle bacilli. It was found that virulent bacilli destroyed the monocytes more rapidly than attenuated bacilli and were able to multiply intracellularly in the surviving cells at a more rapid rate. Heavy infection levels of attenuated bacilli had the same effect on normal monocytes as light infections by virulent organisms. The most severe effect of all bacilli on cells occurred within the first 48 hours. This initial cell death appeared to be the result of a "toxic" effect of relatively small numbers of intracellular bacilli. Thereafter, even with virulent organisms, some monocytes survived and migrated well with large numbers of intracellular multiplying tubercle bacilli. The final death of such cells in tissue culture seemed to be a consequence of mechanical "bursting" of the cell. S. J. SHANE

Growth in HeLa Cells of Tubercle Bacilli from Human Sputum.

C. C. SHEPARD: *Am. Rev. Tuberc.*, 77: 423, 1958.

Tubercle bacilli in sputum concentrates, when inoculated into HeLa cells, show essentially the same picture of intracellular growth as that seen with inocula prepared from bacteriologic medium. Of the tubercle bacilli present in the concentrates studied, 50 to 70% were judged capable of growth in HeLa cells. Generation times were estimated to be about two days between the first and third days, and one day between the third and fifth days.

No evidence was obtained that 2% sodium hydroxide was harmful to the bacilli during the concentration procedure. Concentration by trypsin digestion at neutral reaction gave tubercle bacilli with substantially the same "viability rates" and generation times. When tubercle bacilli from sputum were inoculated into cells which had received 1000 r of radiation, they grew at about the same rates as they did in nonirradiated cells. HeLa cell cultures were compared with bacteriologic media for their usefulness in the laboratory diagnosis of tuberculosis. The tissue cultures were less sensitive to small numbers of tubercle bacilli, and they demanded more technical skills. The result was obtained quickly, however, and the mycobacterial growth pattern was that seen only with pathogenic mammalian tubercle bacilli. This procedure would therefore appear to have a certain restricted field of application.

S. J. SHANE

PUBLIC HEALTH

Increase, Constancy and Decrease of Cancer Incidence in France and Switzerland *(In German)*.

H. R. SCHINZ AND T. REICH: *Deutsche med. Wchnschr.*, 83: 487, 1958.

These authors apply a method which they have previously described to cancer-mortality statistics. Studying the rise and fall in incidence of cancer of 12 different organs, they came to the following conclusions: (1) When cancer of a certain organ is on the increase, the earliest age at which it affects people shifts towards the younger age group. (2) When a type of cancer is on the decrease, the age of the youngest groups affected rises. (3) When a cancer has remained unchanged in its incidence, the age of onset does not change. Having tested these findings statistically in Switzerland by comparing the mortality figures for 1926-30 with those for 1950-54, they checked the same figures for France (1948 compared with 1955). Again it was shown that the shift in age of mortality runs parallel with the incidence of the disease.

Thus, increasingly, younger people are affected by cancer of the lung, which is on the increase. Conversely, cancer of the œsophagus, stomach and colon is affecting older people than previously, and is shown to be on the decrease in both France and Switzerland. Cancer of the uterus has remained unchanged both as regards its incidence and age of earliest mortality. W. GROBIN

INDUSTRIAL MEDICINE

The Problem of Isolating the Noise-Susceptible Individual.

R. CARHART: *Am. Indust. Hyg. A. Quart.*, 18: 335, 1957.

Extensive research must be continued if the problem of isolating the noise-susceptible person is to be solved. The noise-susceptible worker is one who suffers handicapping hearing losses more quickly than his companions do when under equivalent noise exposure. The task of finding such workers is important as they constitute the group from which compensation claims are most likely to arise and for whom awards are likely to be greatest. Their discovery has been impeded by: (1) limited current knowledge regarding the nature and the relative incidence of proneness to acoustic trauma; and (2) unvalidated test procedures for detecting this proneness prior to job placement.

Contemporary concepts regarding the nature of noise-susceptibility are confused. Research is needed to establish to what degree it is a continuing predisposition and to what degree it is transiently induced by temporary or biochemical states. At the present time, continuing surveillance of all who work in environments of intense sound is indicated.

Definitive tests are needed to identify the condition (predisposition for noise-damage). Detailed discussion is given regarding the following criteria: (1) measurement of temporary threshold shift, (2) measurement of oral overload, and (3) measurement of reaction to cumulative auditory stimulation. Final judgment on each procedure must await field validation.

MARGARET H. WILTON

Canad. M. A. J.
June 15, 1958, vol. 78

OBITUARIES

Le DR BRUNO CLOUTIER, de St-Jean-Port-Joli, est décédé récemment à l'âge de 57 ans et quatre mois. Il était né à St-Zéphirin-de-Courval, comté d'Yamaska, le 14 décembre 1900.

Il fit ses études au Séminaire de Nicolet, de 1915 à 1923, et gradua comme docteur en médecine à l'Université Laval, en 1929. Il pratiqua deux ans à St-Aubert, 17 ans à St-Pamphile de l'Islet et depuis à St-Jean-Port-Joli.

DR. JOHN ADAM CREIGHTON, aged 85, died in Calgary, at Colonel Belcher Hospital, on April 27, after a long illness. He was born at Wingham, Ont., taking his formal education there; he then attended the University of Manitoba. In his early life he was a school teacher.

Dr. Creighton began to practise as a doctor of medicine in 1903, when he moved to Nanton, Alta. He operated a drug store in Nanton for several years before retiring in 1955.

He is survived by a son and a daughter.

DR. EUGENE GAULIN, aged 63, died at his home in Ottawa on April 27, after a short illness. He was born in Ottawa, and was educated at Ottawa University, Ste. Thérése College and the University of Montreal. He graduated from the University in 1922. Later he did postgraduate work in Paris hospitals. Dr. Gaulin was a member of many associations and one of the founders of the University of Ottawa School of Medicine.

He is survived by his widow, three sons and three daughters.

DR. WILLIAM HIRD, aged 95, died in Beaconsfield, Quebec, on May 5. He was one of the pioneer country doctors of Wallaceburg, Ont., and gained distinction for his constant efforts during the influenza epidemic of 1918.

Dr. Hird was born in Whitby, Ont., and was an alumnus of the University of Toronto. He extended his studies of medicine in Scotland, England and Australia. He carried out his work as a medical practitioner in and around Wallaceburg for 65 years. After his wife's death, he went to live with a daughter in Quebec.

He is survived by three daughters.

DR. W. PORTE MARSHALL, aged 57, died in London, England, on April 27; he had been ill for some time. He was born in Belleville, Ont., and was a graduate of the University of Toronto. Dr. Marshall took postgraduate studies at the Hôtel-Dieu, Windsor, and Toronto Western Hospital.

He was in practice in Colborne, Ont., until January 1940, when he enlisted in the Canadian Army Medical Corps and went overseas until 1945. In 1946 he became associated with the Department of Health and Welfare in London, England, a post he held until the time of his death.

Dr. Marshall is survived by his widow, two sons, and a daughter.

DR. JACOB ISRAEL ROSSMAN, aged 43, died in New York Hospital on May 10.

He was born in Toronto, and educated at Port Colborne High School, graduating as an honour student. In 1939, he graduated from the University of Toronto. He took postgraduate work in Toronto and United States cities, attaining his F.R.C.S. in Edinburgh, Scotland.

Dr. Rossman had been practising in Ottawa until he was taken ill last fall.

He is survived by his widow, a daughter and two sons.

DR. GARNET R. SCHAMEHORN, aged 37, died suddenly in Kingston, Ont., on March 15. He was born at Napanee, and received part of his education in Prince Edward County. He graduated from Queen's University, interning in Toronto, and followed this with a year's postgraduate study in Sunnybrook Hospital.

During the war he trained at Mountain View Airport, and received his wings. As an aircrew navigator he served in England and Africa.

Dr. Schamehorn is survived by his widow, a brother and a sister.

FORTHCOMING MEETINGS

CANADA

CANADIAN PSYCHIATRIC ASSOCIATION, Annual Meeting, Halifax, Nova Scotia. (Dr. Charles Roberts, P.O. Box 6034, Montreal, Que.) June 20-21, 1958.

INTERNATIONAL FERTILITY ASSOCIATION, Windsor Hotel, Montreal, Que. (Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield 8, Mass., U.S.A.) June 20-22, 1958.

INTERNATIONAL FEDERATION OF GYNÆCOLOGY AND OBSTETRICS, 2nd Congress, Montreal, P.Q. (Professor Léon Gérin-Lajoie, Suite 313, 1414 Drummond Street, Montreal, P.Q.) June 22-28, 1958.

10TH INTERNATIONAL CONGRESS OF GENETICS, Montreal, P.Q. (Mr. J. W. Boyes, General Secretary, 10th International Congress of Genetics, McGill University, Montreal, P.Q.) August 20-27, 1958.

L'ASSOCIATION DES MÉDECINS DE LANGUE FRANÇAISE DU CANADA, 28ième congrès, Saint-André-sur-Mer, Nouveau-Brunswick. (Secrétariat: 326 est, boulevard Saint-Joseph, Montréal 12, P.Q.) 11, 12 et 13 septembre 1958.

UNITED STATES

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, San Francisco, California. (Dr. George Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 23-27, 1958.

INTER-SOCIETY CYTOLOGY COUNCIL, Annual Scientific Meeting. Hotel Statler, New York, N.Y. (Dr. Paul F. Fletcher, Secretary, 634 North Grand Avenue, St. Louis 3, Missouri.) November 13-15, 1958.

OTHER COUNTRIES

SEVENTH INTERNATIONAL CANCER CONGRESS, Royal Festival Hall, London, England. (Secretary-General, 7th International Cancer Congress, 45 Lincoln's Inn Fields, London, W.C.2, England.) July 6-12, 1958.

CONGRESS OF MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION, Bedford College, Regents Park, London, England. (Dr. Janet Aitken, 30a Acacia Road, London, N.W.8, England.) July 15-21, 1958.

INTERNATIONAL UNION OF BIOLOGICAL SCIENCES, London, England. (Chairman, Division of Biology and Agriculture, National Research Council, 2101 Constitution Ave., N.W., Washington 25, D.C., U.S.A.) July 16-23, 1958.

SIXTH PAN AMERICAN CONGRESS OF OTO-RHINO-LARYNGOLOGY AND BRONCHOESOPHAGOLOGY, Rio de Janeiro, Brazil. (Dr. Walter Benevides, Caixa Postal 2838, Rio de Janeiro, Brazil.) August 10-16, 1958.

PROVINCIAL NEWS

BRITISH COLUMBIA

Dr. E. C. McCoy of Vancouver was elected chairman of the College of General Practice of Canada at the group's Winnipeg convention. Other officers of the College are Dr. P. B. Rose of Edmonton, president, Dr. Laurent Mailloux, treasurer, and Dr. W. V. Johnston, Toronto, executive director.

The Red Cross drive for funds in B.C. is within 30% of its goal of $700,000, over $500,000 having been so far subscribed.

The annual spring meeting of the B.C. Surgical Society was held at Harrison Hot Springs on May 1, under the presidency of Dr. J. W. Frost of Vancouver. The guest speaker was Dr. Frank Glenn, professor of surgery at Cornell Medical College, New York.

The Department of Physiology at the University of British Columbia has been conducting research into defence against atomic radiation, under the terms of a grant made by the Defence Research Council to Dr. Harold Copp, head of the department.

Dr. Copp and Dr. Carl F. Cramer, his assistant in the department, have been directing their attention especially to the question of radioactive strontium, which is so deadly in its effect on bones. According to reports in the press, these two scientists have evolved a method of removing the strontium from the body, if the remedy is applied immediately. So far the experimental work has been confined to rats, but it is planned to undertake human tests, under the most careful precautions, if permission can be obtained from Ottawa. Dr. Cramer, who came to U.B.C. 3½ years ago from New Mexico, has been conducting the experiments on strontium extraction by a high phosphorus diet, which causes removal of the strontium.

Dr. A. M. Gee, director of mental health services of the province, has retired from the service. This is regarded as a heavy blow by those associated with him, especially the staff at Essondale Mental Hospital, where he has been working for 34 years, and where he became the head of the institution after the retirement of Dr. A. W. Crease some years ago. Dr. Gee is recognized as an outstanding psychiatrist. Three other psychiatrists have resigned from Essondale. Dr. Robert Halliday and Dr. Neville Mason Brown have taken up private practice, and Dr. Frank Edwards has moved to an Alberta hospital.

The big hospitals are holding graduating ceremonies just now, and the first one to do so on the Lower Mainland was the Royal Columbian Hospital, where 66 nurses received their medals. St. Paul's Hospital in Vancouver followed next, with 117 nurses graduating. There were other graduations, for eight laboratory technicians of whom two are nuns, and three x-ray technicians. The Vancouver General, last but by no means least, brings up the rear. We have not the numbers available at the time of writing, but naturally it will have the largest group of graduates.

A considerable advance is to be made in the care of handicapped children suffering from chronic ailments in the establishment of a "Children's Village". This will be brought about when the Vancouver Preventorium's new buildings are completed in June. The Vancouver Preventorium has been in existence for nearly 30 years, in a 15-acre area in the eastern part of Vancouver. It was established to take care of children who had been exposed to tuberculosis and could not lead a normal school life and later to take care of active cases in children. Education was provided and special care of every kind, and the Preventorium has done magnificent work all these years. It still treats tuberculous children, but the village will be dedicated to the care of all children suffering from chronic ailments.

Dr. W. H. Hatfield, so well known in B.C. as the former director of the Department of Chest Diseases of the Provincial Public Health Department, is the president of the Preventorium, and has explained that the village will consist of cottages, which will be added to as they are needed. Each cottage will be in the care of a "mother". There will be a central school, dining room and recreation unit, and many other facilities.

The new Preventorium, which cost $600,000, has developed from a donation of $150,000 from the Mrs. Begg estate; other large donations were made by the Agnes Scott Kay estate and the B.C. Tuberculosis Society.

The Rotary Club of Dawson Creek is sponsoring a drive for a new health unit building which will cost $50,000 or more. Funds will be raised partly by this drive, and the federal and provincial governments will each contribute money towards the project. It is hoped that the unit will be ready by the fall.

The Board of Trade of Kamloops and district has launched a campaign to have Tranquille Sanatorium converted to a mental health centre.

Tranquille Sanatorium has a long and honourable history. It was established in the nineteen-twenties, mainly as the result of the work of Dr. C. H. Vrooman, one of B.C.'s great men in the field of tuberculosis. He was succeeded by Dr. Lapp and later by Dr. H. A. Stalker, both of whom fully maintained the high standard set by Dr. Vrooman. Of late, the work in tuberculosis has been centred largely on the coast, and the Tranquille Sanatorium has largely fallen into

Canad. M. A. J.
June 15, 1958, vol. 78

disuse. The residents of this area feel that the province has too much money tied up in equipment and buildings for it to be allowed to be closed completely, and point out that the need for mental health units in the province is very great and that Tranquille would be an ideal location for this work.

A most tragic loss befell the profession here, and especially the Vancouver area, when Dr. J. A. McMillan was killed in an air crash; his wife was killed with him. Dr. McMillan, who was a highly skilled air pilot and had flown for many years, was flying his own machine; he was on the way to speak at a medical meeting at Phoenix, Arizona, on the subject "The Flying Physician". Dr. McMillan was an ardent advocate of the use by doctors of planes, and of their learning to fly. He was an intrepid as well as a skilful pilot, and was immensely popular with all his colleagues. Dr. and Mrs. McMillan leave three small sons.

J. H. MACDERMOT

Dr. Robert B. Kerr, head of the department of medicine at the University of British Columbia, has been appointed to the Sir Arthur Sims Commonwealth Travelling Professorship for 1959. He will teach at various medical centres in Great Britain and Africa during the summer and early fall.

ALBERTA

Dr. H. E. Rawlinson, professor of anatomy at the University of Alberta, is the president of the Edmonton Academy of Medicine for 1958. Dr. Rawlinson, who is vice-president of the Canadian Cancer Society and has done considerable research on the subject, chose for the title of his presidential address, "Hormonal Factors in Mammary Cancer."

The other members of the Academy executive are: Dr. H. L. Richard, 1st vice-president; Dr. S. Hanson, 2nd vice-president; Dr. J. R. Kelly; Dr. E. F. Foy, treasurer; and Drs. W. S. Anderson, D. F. Cameron and F. D. Conroy, executive.

Dr. W. C. MacKenzie, professor of surgery at the University of Alberta, was awarded the first prize for the best moving picture of an operation submitted to the American College of Surgeons. Dr. MacKenzie is a member of the Board of Regents of the College.

Dr. J. Tuba of the biochemistry staff of the University of Alberta has been named recipient of a grant from the Nuffield Foundation to enable him to visit various European institutions to study the methods used in teaching biochemistry. The period of the fellowship is the summer of 1959. For this year Dr. Tuba receives a grant from the National Cancer Institute of Canada to attend the Third Biennial Canadian Cancer Research Conference.

The second annual Interprovincial Physicians' Bonspiel was held in Saskatoon the first week-end in April. Nine rinks from Alberta and six from Saskatchewan were entered. Competition took the form of a round robin, winners of the two sections being Dr. Lees of Edmonton and Dr. Collins of Saskatoon. In the finals Dr. Lees won in a very close game, thus holding the championship he had won in 1957. Members of Dr. Lees' rink were the same as last year: Dr. M. K. Young, third; Dr. F. G. Day, second; and Dr. T. S. Wilson, lead. Dr. A. F. Anderson, of Edmonton, who donated the cup was present for the bonspiel and presented the trophy at the banquet which wound up the occasion.

Next year's bonspiel will be held in Lethbridge and it is hoped that rinks from Manitoba and British Columbia will compete.

Dr. Clark T. Leavitt, a fellow in medicine in the Mayo Foundation at Rochester, Minnesota, has been appointed an assistant to the staff of the Mayo Clinic. Dr. Leavitt is a 1954 graduate of the University of Alberta School of Medicine.

W. B. PARSONS

MANITOBA

Dr. Cecil G. Sheps, a native of Winnipeg and recently general director of Beth Israel Hospital, Boston, Mass., has been promoted to clinical professor of preventive medicine, Harvard University.

Dr. Sheps graduated from the University of Manitoba in 1936, and formerly practised in Winnipeg. He was also associated with the provincial and city health departments.

ONTARIO

The world's foremost scientific authority on alcoholism, Dr. E. M. Jellinek, creator and still secretary of the World Health Organization's International Institute for Research on Problems of Alcohol, is being brought to Canada next fall by the Alcoholism Research Foundation of Ontario and the Alcoholism Foundation of Alberta to continue his studies for two years as an associate in the Department of Psychiatry, University of Toronto.

Dr. Jellinek was (with Dr. H. W. Haggard) the co-founder of both the Yale *Quarterly Journal of Studies on Alcohol* (1940) and the Yale Center of Alcohol Studies (1943), and was from 1941 to 1952 associate professor of applied physiology at Yale, after which he went to the World Health Organization in Geneva, Switzerland.

Dr. Edmund R. McCluskey, who graduated from the University of Toronto in 1923 and is professor and head of the department of pediatrics, University of Pittsburgh, has been named vice-chancellor of the schools of the health professions at the University of Pittsburgh. The appointment, effective July 1, is the culmination of a wide search for a new leader for the university's rapidly developing health center.

In his new post, Dr. McCluskey will coordinate the efforts of the many hospitals and clinics affiliated with and making up the university health center.

CANADIAN ARMED FORCES

Col. E. H. Ainslie, formerly Senior Consultant to the Director General Medical Services (Army), and Group Capt. G. D. Caldbick, formerly Deputy Director General Medical Services (Air) Professional, have been appointed to the staff of the Director General of Joint Medical Services as Consultants.

Brigadier S. G. U. Shier, D.G.M.S. (Army), recently returned from a trip to Europe. While there he visited the Canadian Brigade in Germany and reviewed the training of Medical Corps personnel, as well as the arrangements for medical care of the servicemen and their families. Later, as the representative of Canada's Armed Forces Medical Services, he attended the annual medical conference of SHAPE (the military component of the NATO organization) in Paris. Returning to Canada via London, he made a liaison visit to the War Office for discussions with the British Director General of Army Medical Services and had the honour of inspecting a recruit training class of approximately 300 at the R.A.M.C. Depot at Crookham near Aldershot.

A number of R.C.A.M.C. officers have recently attended short courses in the management of mass casualties at U.S. Army installations. Col. C. B. Caswell, Command Medical Officer, Eastern Command, and Col. K. J. Coates, Command Medical Officer, Prairie Command, took the course at Brooke Army Medical Center, San Antonio, Texas. Lt.-Col. J. P. McCabe; Lt.-Col. A. G. McLaren, Area Medical Officer, British Columbia Area; Lt.-Col. W. A. Reed, Commanding Officer, 4 Field Ambulance R.C.A.M.C., Camp Borden, Ontario; Lt.-Col. R. J. A. Robitaille, Commanding Officer, 2 Field Ambulance R.C.A.M.C., Camp Valcartier, P.Q., and Major F. R. Cullen, Deputy Command Medical Officer, Headquarters, R.C.A.M.C., Prairie Command, attended a similar course at the Walter Reed Army Institute of Research, Washington, D.C. These courses are now undergoing a reorientation, with more emphasis on the preventive aspects of rehabilitation following mass disaster.

BOOK REVIEWS

THE SPECIALTIES IN GENERAL PRACTICE. Edited by Russell L. Cecil, Emeritus Professor of Clinical Medicine, Cornell University Medical College, New York City, and Howard F. Conn, Department of Physiology, Baylor University College of Medicine, Houston, Texas. 780 pp. Illust. 2nd ed. W. B. Saunders Company, Philadelphia and London, 1957. $16.00.

The large demand for the first edition of this book has necessitated the publishing of a second edition. This in itself is an indication of its usefulness. As the preface says, the contributors are all outstanding men in their field and professors in leading medical schools in the U.S.A. The first impression is one of completeness with due regard for the needs of the general practitioner.

The section on minor surgery is quite full and well illustrated. The two chapters on orthopædics and on fractures and dislocations, and the chapter on urology, seem to offer everything that a general practitioner could ever want in these fields. However, gynæcology receives rather sparse treatment and many conditions within the scope of the general practitioner have been omitted. On the other hand, the obstetrics section is full and practical. It is interesting to note that, in the discussion of the diseases of the anus, rectum and colon, the author condemns the office treatment of hæmorrhoids by injection. This chapter is exceptionally full without being too technical for the general practitioner who has much to do with these diseases.

The discussion of pædiatrics, which is so recent as to include poliomyelitis immunization, is adequate and well illustrated. The chapter on ophthalmology is a very salutary one for the general practitioner, who is apt to forget about some of these conditions. The illustrations here are excellent. However, the section on the nose and throat, although fully dealt with in the text, is rather poorly illustrated from the standpoint of the non-specialist. The diseases of the larynx, bronchus and œsophagus are very well handled and well illustrated, as could be expected from Professor Chevalier Jackson.

The section on the ear again gives information which should be in the hands of every general practitioner, even though he probably would not undertake many of the procedures described.

Any section on dermatology and syphilis is usually made or marred by its pictures. The pictures here are very good. Although they are in black and white, they quite satisfactorily illustrate the conditions described.

This reviewer was especially struck with the chapter on psychiatry. This section should be read by every man in general practice. Besides the usual psychiatric diseases, other associated problems are well discussed, such as alcoholism, the problems of childhood, the problems of the sex life from childhood through adulthood, and so forth. The management of patients with fatal or chronic illnesses is also treated in a very sympathetic manner. The general practitioner can learn a great deal from the author's description of how to interview the anxious patient. This chapter alone is worth the price of the whole book.

It is rather surprising, however, to discover that a book on general practice does not include a discussion of the diseases of the stomach and small bowel, nor is there any section on the glands of internal secretion. Diseases of the liver, gallbladder and pancreas, including diabetes, are not even mentioned. One would expect, too, in a book of this size a chapter on geriatrics. With these exceptions, the book gives a postgraduate course to any general practitioner who will take the time to read its very well written pages.

CLINICAL ORTHOPÆDICS, Number 9. Anthony F. DePalma, Philadelphia, Editor-in-Chief. 353 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1957. $7.50.

As in former numbers of this excellent series, the Editor-in-Chief has compiled groups of articles of related interests. The first section of this number is devoted to the pathologic physiology of metabolic bone disorders, including a wide variety of conditions, such as rickets, osteomalacia, osteoporosis, and osteosclerosis. The second section is entitled general orthopædics, and includes articles on such subjects as scoliosis, skin grafts in hand surgery, prosthetics in child amputees and avulsion of the tibial apophysis. The individual authors have presented their ideas clearly, thereby matching the excellent illustrations. The third section, edited by Dr. Jacob Kulowski, includes ten chapters related to the prevention of automobile accidents and is very appropriate in our present era of increasing speed and power on the highways.

This series is a valuable addition to any orthopædic reference library, and the number under review matches its former numbers in quality.

Canad. M. A. J.
June 15, 1958, vol. 78

ORTHOPEDICS FOR THE GENERAL PRACTITIONER. William E. Kenney, Orthopedic Surgeon, Truesdale Hospital, Fall River, Mass., and Carroll B. Larson, Professor of Orthopedic Surgery, State University of Iowa, Iowa City. 413 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1957. $11.50.

The reviewer has nothing but praise for this splendid volume. Its 400 pages are packed with the kind of information the general practitioner would want, and it may well be that a good many specialists would at least have their memories refreshed by a perusal of it.

The book is organized in such manner as to minimize the length of time required to find some information on a given problem. Each chapter deals with a given region of the body. A table gives the most likely diagnoses for a given set of complaints referable to that region, and then one may quickly turn to the discussion of that particular condition. Diagnosis and correct treatment are here the things of paramount importance. Every paragraph is practical in its point of view, and there is no excessive verbiage. As is appropriate, the common conditions are described in detail, and the rarer ones are discussed briefly. The first 110 pages of text present a concise and lucid description of orthopædic conditions peculiar to childhood, and the assignment of disorders to particular age levels is very helpful. Following the chapters on the various regions, there are short chapters covering osteomyelitis, arthritis, unusual diseases of bone, and bone tumours.

The authors are to be commended for a work which reflects much thought, careful selection and organization of material and which, in the reviewer's opinion, fulfils admirably its avowed purpose.

CHRONIC ILLNESS IN THE UNITED STATES. VOL. IV: CHRONIC ILLNESS IN A LARGE CITY. The Baltimore Study. Commission on Chronic Illness. 620 pp. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass.; S. J. Reginald Saunders and Company Limited, Toronto, 1958. $8.80.

It is a pleasure to read this excellent book, which is well written and reported. The report covers the questionnaire and home visiting study of a selected sample of the population of Baltimore, comprising 11,574 persons. Then a second group of persons were invited for a multiple health screening survey. Of these, only 29% or 2024 were examined. A final group of 809 persons were subjected to a full medical examination. In addition comprehensive studies were carried out on the functional ability of disabled persons, the days of disability, the needs for care and rehabilitation, the social and economic implications, and last but certainly not least, the attitudes of patients towards their diseases. Amongst many other matters discussed, this investigation has shown that household survey reports do not give a reliable picture of disease, as one might expect. The only reliable method is by competent medical examination. A detailed and most useful discussion is given of all methods used in the study, from statistical sampling to methods of sight testing and electrocardiographic interpretation.

An especially interesting chapter is on the needs of a high disability group. Next to medical care and nursing supervision, the greatest need was for diet therapy, not only in weight reduction, but for diabetes and a smaller proportion for low salt and other special diets. It is pleasant to note that the standard tables used for diagnosis of obesity were those developed by Dr. L. B. Pett, Department of National Health and Welfare, Ottawa.

This fine piece of work should be carefully studied not only by internists and other clinicians interested in chronic disease, but also by those who are at present planning our health services, and by public health experts who wish to expand their activities into the field of personal preventive medicine and rehabilitation.

FUNDAMENTALS OF ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY. Lawrence E. Lamb, Air University, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas. 142 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $10.50.

This book is designed to present "the basic fundamentals of electrocardiography and vectorcardiography." The author properly emphasizes that rule-of-thumb electrocardiography is no longer a satisfactory approach to diagnosis and that a good grounding in the fundamentals of the distribution of electrical potentials in a volume conductor is essential to the understanding of these phenomena. He would no doubt agree also that it is mandatory for the research worker in this field.

The introductory chapter deals with the concept of the vector. The next three chapters are devoted to the relation of the cell to electrical potential, to the excitation of the heart as a whole, and to the fundamentals of conductors. The chapter on instruments is too sketchy to be of much value. The discussion on the fundamentals of leads is valuable. The relationship between the scalar and the vector methods of cardiographic analysis is described at length. A very useful table for the calculation of the spatial angle is included. The principles of vectorcardiography are then outlined. The subsequent chapters deal briefly with cardiac enlargement, conduction defects, pericarditis, infarction and the effects of various drugs as related to the electrocardiogram and the vectorcardiogram. Arrhythmias are mentioned, but inadequately.

This is not the text for the individual who has purchased a machine and is anxious to memorize a few diagnostic patterns in his spare time; there are other texts which will serve that purpose better. It is, however, a good introduction to the fundamentals of electrocardiography and vectorcardiography for the person who wants a satisfactory foundation in this complex and growing field.

PRINCIPLES OF OPHTHALMOSCOPY. John K. Erbaugh, Norristown State Hospital, Norristown, Pennsylvania. 69 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $6.00.

This book would appear to be written for general practitioners. It describes the steps in ophthalmoscopic examination and the significance of certain findings in the interior of the eye. At the end of the book is a small appendix discussing the construction of the ophthalmoscope and how it works.

Those who would like a quick review of some of the simple points concerning ophthalmoscopy could use this book. Those who wish proficiency in ophthalmoscopy must seek one of the larger texts.

(Continued on page 986)

Another clinical evaluation of Mio-Pressin* in hypertension

Salient observations:

- "Since hypertension may be caused by a variety of factors influencing several body mechanisms, it is generally believed that a combination of drugs, each having a different site of action, is more likely to be effective than any one drug alone."

- "Eighty-nine per cent of the patients [in this evaluation] had become normotensive by the conclusion of the study."

Smith, C.W., and Thomas, C.G.:
Am. Pract. & Digest Treat.
8:920 (June) 1957.

'Mio-Pressin'—a balanced combination of rauwolfia, protoveratrine and Dibenzyline*—for moderately severe to severe hypertension, in two dosage strengths: No. 2 (standard strength) and No. 1 (half strength).

Smith Kline & French · Montreal 9

6140

*Reg. Can. T. M. Off.

Canad. M. A. J.
June 15, 1958, vol. 78

(Continued from page 984)

A MENTAL HEALTH HANDBOOK. Ian Skottowe, Psychiatrist, the Warneford and Park Hospitals, Oxford, England. 196 pp. Edward Arnold (Publishers) Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1957. $3.60.

The purpose of a handbook is to present material relevant to a specific subject in a direct and factual manner. In this small volume, Dr. Skottowe has successfully managed to do this in his coverage of the field of mental health. Even though the author develops his notions of mental health problems and services as they refer to the situation in Great Britain in particular, it is evident that, in general, the principles apply to the mental health field as a whole.

There are eight chapters in this volume, but the areas covered can be considered under four main headings, viz., (1) the development of mental health services in Great Britain; (2) the concept of mental health, with a description of factors related to personality development, and the varieties of mental ill-health; (3) mental health problems in the community, including therapeutic and preventive aspects; and (4) suggestions and recommendations for future developments in the mental health service.

The section dealing with the development of mental health services as part of the National Health Service in Great Britain gives a historical account of the legislative changes that have occurred since the nineteenth century as background to the services operating at present. It highlights the complexity and diversity of this problem—but clearly emphasizes the need for flexible organization to include all professional and lay groups (such as public health personnel, family doctors, welfare workers, health visitors and volunteers) in the over-all scheme of mental health service. In this context, the immediate and long-term aims of mental health services are defined. The section dealing with personality development and clinical psychiatry provides a helpful, although rather limited and elementary scientific background to the subject of mental health. The main criticism of this part of the book is that it reflects the author's point of view rather than a cross-section of modern psychiatric thinking. Specifically, the author puts rather exaggerated emphasis on constitutional factors—and this tends to create a somewhat unbalanced picture. Since this book is intended for those with limited psychiatric experience, such as general practitioners, social workers and lay groups, a more eclectic approach would probably have been preferable.

The chapters concerned with mental health problems in the community are presented in a skilful and lucid manner. The importance of recognizing mental problems is emphasized—and here the roles that could be played by public health personnel, school teachers, welfare officers, and probation officers are of primary importance. Problems related to disturbed families, neglected children, children handicapped by mental subnormality, specific physical or emotional disabilities, mental health in industry, patients discharged from mental hospitals and others are presented in clear and constructive terms. The suggestions for prevention and treatment are made realistically with a nice balance between a positive program and the limitations that inevitably exist.

The final chapter attempts to indicate ways to integrate mental health services, utilizing the experience gained since the National Health Service was inaugurated. The author puts forward recommendations designed to: (a) establish closer liaison between key persons (experts) concerned with clinical and preventive services, (b) foster relationships between hospitals, clinics and community agencies around clinical problems, (c) examine and revise functions and design of mental hospitals, (d) define the place of psychiatric units and children's psychiatric services in the mental health service scheme, and (e) meet the problems of forensic patients.

Further, there is recommendation for provision of training facilities of personnel, particularly psychiatric social workers, judicious utilization of techniques for public education and the fostering of research.

As a source of valuable information, useful suggestion and provocative ideas regarding the field of mental health, this book is indeed worthwhile for all those interested in this area.

CEREBRAL LIPIDOSES. A Symposium. Chairman, L. van Bogaert, Director, Department of Neurology and Neuropathology, Institut Bunge, Antwerp. Edited by J. N. Cummings, London, and A. Lowenthal, Antwerp. 212 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $10.25.

The 20 papers printed in this volume were given at a meeting held in Antwerp in July 1955 and organized by the Inter-University Foundation of Neuropathological Research.

The papers deal with the broad subject of "demyelinating diseases" as they are now being intensively studied by histologists, histochemists and chemists. The reports of these workers indicate that in the degeneration of the myelin sheaths the constituent lipoid substances may be capable of specific histological staining. By the combination of chemical studies with these refined histochemical methods, the chemical constitution of an area of demyelinated white matter may prove to be a valuable aid in the elucidation of the causes of demyelination.

The book is also useful in providing detailed descriptions of the techniques which have been evolved for the chemical examination of brain tissues.

MENTAL DEPRESSIONS AND THEIR TREATMENT. Samuel Henry Kraines, Diplomate, American Board of Neurology and Psychiatry. 555 pp. Illust. Brett-Macmillan Ltd., Toronto, 1957. $8.00.

Dr. Kraines has an eclectic approach and a belief that manic-depressive illness has an organic basic. He considers it due to a combination of hereditary susceptibility and a physiologic precipitating factor (often hormonal). Disturbed function in the diencephalic region is believed to be the mechanism at fault. He presents suggestive evidence in support of this theory.

The early chapters include an excellent study of normal moods and of psychopathology. The statistical reviews, clinical descriptions and outline for treatment are good. The discussion of electroshock therapy is marred by the author's personal rejection of succinylcholine, in favour of longer acting curare-like preparations.

There is a certain amount of repetition and more examples from patients' records than are necessary.

(Continued on page 988)

Canad. M. A. J.
June 15, 1958, vol. 78

(Continued from page 986)

THE PRINCIPLES AND METHOD OF PHYSICAL DIAGNOSIS. Simon S. Leopold, University of Pennsylvania. With a chapter on Sounds from the Thorax: Acoustic Principles, by S. Reid Warren. 537 pp. Illust. 2nd ed. W. B. Saunders Company, Philadelphia and London, 1957.

The writing of a book on history taking and physical examination is a task which in some respects is even more challenging than writing about disease as such. While there is general agreement as to the principles involved in extracting the maximum information from the patient, there is much room for differences of opinion in the practical application of the details. Each specialty is likely to feel that its own topic is inadequately treated, that some outmoded residua of a past age have been included, and that recent viewpoints on the merit of a given technique have been omitted.

This volume is planned in the conventional way, with the opening chapter on the history, followed by a useful discussion of the psychiatric appraisal. A detailed description of the examination of the various systems occupies the rest of the text, which ends with a special chapter on the examination of children. The illustrations are numerous and useful, although as with all books of this type there is an understandable tendency to portray the most extreme examples of abnormality. An interesting feature, particularly for those of us brought up on Norris and Landis, is the retention of their famous photographs of cross-sections of the cadaver.

Both in writing and in teaching, insufficient attention is often paid to the application of acoustics to the understanding of percussion and auscultation. Here an attempt has been made to remedy this defect but it is successful only in part. The acoustical principles are clearly set forth but their practical use is not satisfactorily presented, perhaps because this chapter is written by an engineer. Figure 185 is printed upside down.

One might take exception to some of the statements. The terminology of pulmonary adventitious sounds is not that commonly used. Rhonchi are mentioned only in connection with children. The cardiothoracic index (ratio) is not a useful measure of cardiac enlargement. The implication that one can percuss satisfactorily the upper and right borders of the heart is evidence of an optimism not shared by most cardiologists.

These are minor criticisms in a generally satisfactory textbook.

JUVENILE EPILEPSY. Report of a Study Group. WHO Technical Report Series No. 130. 44 pp. World Health Organization, Palais des Nations, Geneva, 1957. $0.30.

This report upon juvenile epilepsy appears under the auspices of the World Health Organization. It was written by a distinguished study group, is directed at those responsible for the organization of public health services and contains much to interest a wider audience. It is concerned with those patients who suffer from so-called centrencephalic (idiopathic, cryptogenic) epilepsy and from temporal lobe epilepsy, or about 80% of child epileptics. The term "juvenile" covers the period from birth to school-leaving age.

The first half of the report discusses, shortly and clearly, prevalence, pathophysiology and psychological and clinical phenomena. This is a good guide to the statistics and terminology of the subject and an authoritative summary of present knowledge, particularly of the genetic aspects, relevant to the report.

The second half deals, in general principles, with the application of this knowledge and is based on the experience of units in Sweden, France and the United Kingdom. It suggests the establishment, within existing organizations, of "centres" for accurate diagnosis and to ensure the continuous supervision of these children. The important educational work of such a centre is stressed and, in part for this purpose, the case-conference technique is advocated. Social workers, school medical officers and teachers are central to the successful management of these children and their role is discussed in some detail. The principles of medical management are outlined and advice is given upon the handling of the family and upon the common problems, including employment, of epileptics. A useful bibliography is appended. Within its set limits, this report gives a succinct, helpful and up-to-date account of the management of the group of patients with whom it deals. It is not a complete account of every aspect of epilepsy in children but contains much useful information and advice. It will be of value to all who deal with these patients and perhaps indispensable to those to whom it is specifically directed.

TUMOR SURGERY OF THE HEAD AND NECK. Robert S. Pollack, Stanford University School of Medicine, Stanford-San Francisco, California. 101 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1957. $5.00.

In the author's preface, he makes the statement, "Brevity and conciseness have been a major goal—this book is not an encyclopedia—no originality can be claimed or is inferred". These phrases, unfortunately, pretty well sum up the contents of the book. The introductory chapters and those on postoperative care are of interest and are rationally written. The actual space devoted to surgical technique, however, is not enough to cover the subject adequately for the surgeon already doing this type of surgery, nor is the description elementary enough to be of use to the undergraduate student.

This volume would apparently be of use only to the surgical trainee who is interested in this region.

HUMAN BIOCHEMISTRY. Israel S. Kleiner, New York Medical College, and James M. Orten, Wayne State University College of Medicine, Detroit, Michigan. 808 pp. Illust. 5th ed. The C. V. Mosby Company, St. Louis, Mo., 1958. $9.00.

Large sections of this medium-sized textbook of human biochemistry have been either rewritten or revised for the new edition, which carries the name of a new co-author, Dr. James M. Orten of Detroit. The aim of the textbook remains the same, namely, "to produce a volume suitable and useful for the student of medicine, dentistry and cognate disciplines". Discussion of advanced mathematics or organic or physical chemistry is kept to a minimum, and the authors have borne in mind that the textbook might be useful for revision reading by older clinicians.

Sections on metabolism and on blood have been completely rewritten, and large parts of the sections on vitamins and hormones extensively revised.

THE DERMATOLOGIST'S HANDBOOK. Ashton L. Welsh, University of Cincinnati College of Medicine, Cincinnati, Ohio. 427 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $16.50.

This book is a pharmacopœia of medicine, with emphasis on dermatology, designed for dermatologists. Of the 427 pages, 136 are on topical therapy (21 of these concern topical mucous membrane therapy).

The topical therapy portion is primarily a list of formulæ under such chapter headings as cleansing agents, powders, liquids, pastes, ointments, and creams. There is a very brief introduction to each chapter. The formulæ are both new and old, useful and useless, long and short. The contents of many pharmaceutical prescriptions are listed after the U.S.P., N.F. and N.N.R. equivalents. While in general the author warns of possible complications of topical therapy, he has omitted reference to sodium retention and weight gain following the use of applications of 9-α-fluorohydrocortisone. This reviewer doubts that many dermatologists would use 10% salicylic acid on an eczematous dermatitis. Surely the inclusion of patent medicines is not necessary.

The internal therapy portion covers the use of such divers therapeutic agents as chaulmoogra oil, contraceptives (one page), radioactive cortisone and hydrocortisone, and digitalis, as well as the more commonly used agents such as antibiotics, antihistamines and analgesics. Many of these are dealt with in considerable detail, e.g. the various types and stages of malaria which respond to chloroquine. Iron sulfate, by itself, is not listed under hæmatinics. Anabolic stimulants contain 28 ingredients; calcium and vitamin pills, 24.

The last 100 pages cover treatment of poisonings, removal of medicinal stains, a table of normal values, notes on prescription writing, potency units of antibiotics and vitamins, a table on the efficacy of practical antibiotics and a brief outline of some of the dermatological and systemic reactions to therapeutic agents. Then follows a list of names and addresses of manufacturers and distributors. There is a good index. There are neither references nor photographs.

By its very nature, this book will rapidly be out of date. Many new therapeutic agents now available are not included. There is no indication as to the efficacy of the various alternative products described. There is much duplication (e.g. the sulfonamides topically are described in 14 places, internally in another 14 places). The omission of oleo-resin patch tests and oral vaccines for the diagnosis and treatment of pollen dermatitis is noted.

The author has tried to please all of the people all the time. The result would have been much superior if he had discarded all those agents of doubtful value and discussed at greater length those of proven value.

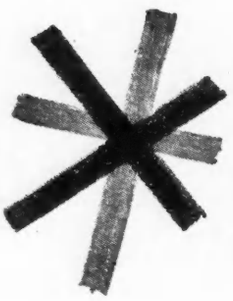
Its size is 11 by 9 inches, it weighs three pounds, and it has 427 pages. Really quite a large handbook!

JOINT ILO/WHO COMMITTEE ON OCCUPATIONAL HEALTH. Third Report. WHO Technical Report Series No. 135. 22 pp. World Health Organization, Palais des Nations, Geneva, 1957. $0.30.

At the third meeting of the Joint ILO/WHO Committee on Occupational Health, whose report has recently been published, the Committee considered the training of physicians in the field of occupational health, the scope and organization of occupational health institutes, and criteria for the recording of medical causes of absenteeism by occupational health services. The Committee began by discussing and listing in general terms the general knowledge required at three levels in occupational health. In the first place they considered the general knowledge required by every physician, which should be taught to him while he is an undergraduate. In the second place they considered the knowledge required by the part-time industrial physician, i.e. the physician whose activity in occupational health is subsidiary to his general practice. Thirdly, they considered the knowledge required by the specialist in occupational health. They recommended that the basic instruction in occupational medicine should be given during the last two years of medical training in medical school; chairs of occupational health should be created in all universities. For the part-time occupational health physician, short courses should be provided in the form of seminars, refresher courses or short practical courses. The specialist in occupational health would require a year's postgraduate course in occupational medicine in a recognized establishment, with the granting of a special diploma.

The Committee considered the establishment of specialized occupational health institutes for teaching, research, and provision of services. They discussed their functions, their association with other organizations such as universities, government departments and industrial firms, and their composition.

The third item on the agenda—criteria for recording of medical absenteeism—was discussed only in general terms, and the report gives no guidance on this subject.



EASIER CONTROL OF SUMMER-TIME ALLERGIES

For the quick relief which ACTH gives in summer-time allergies, with minimal inconvenience to your patient, use Cortrophin-Zinc. Its prolonged action permits maximal response in rose fever, poison ivy, poison oak, sumac, asthma, and other allergic manifestations, with fewer injections. Each injection lasts at least 24 hours in the most acute cases to 48 and even 72 hours in milder cases. And Cortrophin-Zinc is easy to use, being an aqueous suspension which requires no preheating and flows easily through a 26-gauge needle.

CORTROPHIN*-ZINC†

HAY FEVER
POISON IVY
POISON OAK OR SUMAC
SEASONAL ASTHMA
ROSE FEVER

Supplied in 5-cc vials, each cc containing 40 U.S.P. units of corticotropin adsorbed on zinc hydroxide (2.0 mg zinc/cc)

**T.M.—Cortrophin*

†*Patent Pending. Available in other countries as Cortrophine-Z.*

†*Organon brand of Corticotropin-Zinc Hydroxide*

an Organon development

ORGANON INC., *Canadian Branch*, 286 St. Paul St., West, Montreal

. . . without doubt here is a unique method of applying antibiotics for topical use in a dry form—in this case a stable combination of Zinc Bacitracin, Neomycin and Polymyxin 'B'. They are dispersed in ultra-fine powder form (milled to an average particle size of 60 microns) under pressure with an inert gas propellant which is neither toxic nor inflammable. Polybactrin is remarkably economical because of its speedy bactericidal action—bacteriological tests performed demonstrate complete inhibition of gram positive and gram negative organisms on heavily inoculated blood plates—after only a fractional exposure to this antibiotic triad—and equally important, does not induce the development of resistant strains. Furthermore, there are no contra-indications to the use of Polybactrin which has proved to be highly effective in the treatment of contaminated wounds and as a prophylaxis in all branches of surgery . . .

POLYBACTRIN

unique antibiotic powder spray

Each pack contains

Neomycin Sulphate	750 mg.
Polymyxin 'B' Sulphate	150,000 units
Zinc Bacitracin	37,500 units
Propellant (Dichlorotetrafluoroethane)	83.5 g.
Contents	*85 g. approx.*

CALMIC LIMITED: 220 Bay Street, Toronto
Crewe and London, England • Johannesburg, South Africa • Sydney, Australia

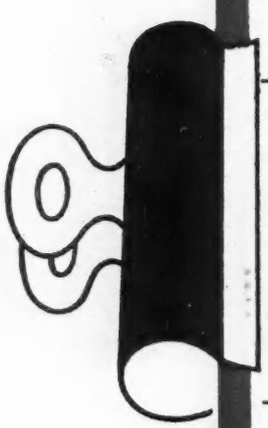
A CLINICAL EVALUATION OF

Signemycin

Oleandomycin – Tetracycline

Response in head and neck infections

Two hundred and eighty-seven patients were treated for infections of the head and neck. Ninety-five and one-half per cent, or 274 cases, responded to Signemycin. The excellent clinical response in the majority of these cases paralleled results obtained by previous investigators.



Head and neck infections: response to Signemycin †

Indications	Total	Successful	Unsuccessful
Abscess, brain	4	4	0
Abscess, peritonsillar (including Ludwig's angina)	16	16	0
EENT Infections (Miscellaneous)	21	18	3
Otitis externa	9	8	1
Otitis media	53	50	3
Parotitis (complications)	5	4	1
Pertussis (complications)	3	3	0
Pharyngitis	37	33	4
Sinusitis	49	49	0
Stomatitis	6	6	0
Submaxillary gland infection	3	3	0
Tonsillitis	68	67	1
Mastoiditis	13	13	0
Total	287	274	13

Successful response rate — 95.5%

Supply:
250 mg capsules (83 mg Oleandomycin, 167 mg Tetracycline)—Bottles of 16 and 100
100 mg capsules (33 mg Oleandomycin and 67 mg Tetracycline)—Bottles of 25 and 100
Oral Suspension 83.3 mg Tetracycline 41.7 mg Oleandomycin 1.5 gram powder—60cc bottles
Intravenous 250 mg vials (83 mg Oleandomycin and 167 mg Tetracycline)
500 mg vials (166 mg Oleandomycin and 334 mg Tetracycline)

Pfizer *Progress through research.*

PFIZER CANADA 5330 Royalmount Avenue, Montreal, Quebec

* TRADEMARK OF CHAS. PFIZER & CO. INC.

† Taken from: A Clinical Evaluation of Signemycin, Report on 2,318 Treated Cases.

MEDICAL NEWS *in Brief*

(Continued from page 960)

COLLEGE OF AMERICAN PATHOLOGISTS

Last year, the College of American Pathologists worked out a plan for an Assembly, in order to improve communications between College officials and practising pathologists. A number of Assemblymen were appointed to provide local and informal contact between the governing body and the general membership, and these Assemblymen met for the first time on October 2, 1957, in New Orleans. Dr. Harold G. Pritzker of Toronto was elected as Assemblyman for Canada, and he now appeals to pathologists everywhere who have problems which they feel should be reported to the College to let him know about them, so that he may as Assemblyman transmit these to the next meeting. Dr. Pritzker's address is New Mount Sinai Hospital, 550 University Avenue, Toronto, Ontario.

BIBLIOGRAPHY OF MEDICAL REVIEWS

The third volume of *Bibliography of Medical Reviews* will appear in June. Review articles listed in Volumes 1 and 2 were gathered as a by-product of the *Current List of Medical Literature* operation and were duplicated in the parent publication in another format. With Volume 3, the collection of review articles was extended to all of the current journals received by the National Library of Medicine. The result has been the inclusion in Volume 3 of approximately 600 non-*Current List* articles along with the 2300 review articles also listed in the *Current List*.

The 1958 volume of the *Bibliography of Medical Reviews* is arranged by subject with a separate author index and will contain approximately 2900 references to review articles in clinical and experimental medicine and allied fields which have appeared largely in 1957. Copies of Volume 3 for 1958 will be available from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., at a price estimated at $1.25.

(Continued on page 46)

MEDICAL NEWS *in brief*

(Continued from page 42)

PASSANO FOUNDATION AWARD FOR 1958

Dr. George W. Corner of the Rockefeller Institute for Medical Research has been selected as the recipient of the $5000 Passano Foundation Award for 1958. On Wednesday evening June 25, during the convention of the American Medical Association in San Francisco, a reception and dinner will be held at the St. Francis Hotel to honour Dr. Corner.

This year's award is presented to Dr. Corner for his research on mammalian anatomy and physiology, with particular emphasis on human reproduction. From 1940 until his retirement in 1955, Dr. Corner was director of the Department of Embryology at the Carnegie Institution. He is currently engaged in writing a history of the Rockefeller Institute for Medical Research.

The Passano Foundation was formed late in 1943, to encourage medical science and research, particularly that having a clinical application. It is sustained by annual contributions from The Williams & Wilkins Company, publishers of medical and scientific books.

—

NEW FILM ON PERIPHERAL VASCULAR DISEASE

Release is announced of a new clinical film entitled "Peripheral Vascular Disease—Physiology and Efficacy of a New Therapeutic Agent". This 16-mm. motion picture in full colour and with sound runs for 32 minutes and is available for showing to medical organizations. It was produced in co-operation with research workers at Western Reserve University and a number of New York centres. The scenario includes a classification of functional and organic occlusive vascular diseases, new methods of evaluating muscle blood flow, and the action on the circulation of a new synthetic adrenaline-like drug, Arlidin, or nylidrin hydrochloride. For information write to the sponsoring company: Arlington-Funk Laboratories, Division U.S. Vitamin Corporation of Canada, Ltd., 1452 Drummond Street, Montreal, Que.

AGRANULOCYTOSIS ASSOCIATED WITH PROMAZINE ADMINISTRATION

Out of three patients with agranulocytosis associated with promazine therapy, reported by Glaser and Adams (*Ann. Int. Med.*, 2: 272, 1958), one died from overwhelming monilial infection and one from acute pulmonary œdema. In all three the drug had been administered for a period of more than four weeks; in two patients, large total dosages were used. In the two fatal cases it is of interest that bone marrow examinations demonstrated complete absence of myeloid elements in one, and only the presence of myeloblasts in the other. Prolonged administration and high dosage have been a factor in all previously reported cases of agranulocytosis associated with various phenothiazine derivatives. This has been reported with chlorpromazine and

with the recently introduced drug Pacatal.

The agranulocytosis may be due to allergy or to direct toxic effect on the marrow. Kracke and Parker in 1934 stressed the importance of a "benzamine group", a combination of benzene ring with N, NH or NH_2 groups, in many of the drugs. This has recently been reemphasized by Dameshek. Promazine possesses such a linkage.

Treatment in all cases reported has included penicillin as well as broad-spectrum antibiotics. Enough data are not yet available for evaluation of the usefulness of steroid therapy. In the small series reported here, the two patients receiving steroid therapy died, one of acute pulmonary œdema and one of moniliasis. This latter complication has not been previously reported, but may be due to the broad-spectrum antibiotics. While the incidence of agranulocytosis is quite low, every physician using these drugs should be cognizant of this possible complication. During long-term therapy, periodic white cell counts should be done, and the patient should be instructed to report early to his physician in case of fever or sore throat. The possible occurrence of fungus overgrowth during antibiotic therapy of agranulocytosis should be watched for.

INTRAVENOUS PROTEIN-FREE PYROGEN AS A POWERFUL FIBRINOLYTIC AGENT

The mechanism of pyrogen-induced fibrinolysis was studied by von Kaulla in 67 persons (*Circulation*, 17: 187, 1958). Two-tenths of a microgram of protein-free pyrogenic lipopolysaccharides from *Salmonella abortus equi* or 300 micrograms from *Escherichia coli* (acetylated form) induced in 60 to 90 minutes after intravenous injection a very marked fibrinolysis lasting for 60 to 240 minutes in man. Clots of samples taken at peak activity (105 minutes) dissolved in less than three hours. There was frequently a reduction of antifibrinolysin activity during the fibrinolytic phase. Concomitant treatment with antipyretics did not diminish the fibrinolytic response. The spontaneous lysis time of euglobulins was prolonged after fibrinolytic activity had subsided. At this time more urofibrinolysokinase was required to induce lysis in the test tube. Euglobulin clots prepared from fibrinolytic samples underwent fibrinogenolysis. Repeated daily injections gradually became less effective in producing fibrinolysis. Induced fibrinolysis in patients with thrombophlebitis gave encouraging results.

HEALTH EDUCATION SUMMER SCHOOL IN U.K.

For those who like to combine professional experience with travel abroad, the Central Council for Health Education in England is holding its 1958 Summer School from August 19 to 29 next at Bishop Otter College, Chichester. This school will be organized as a study conference on the theme "The Science and Art of Health Education". A large number of doctors, nurses, health inspectors, teachers, industrial welfare workers and others from overseas as well

(Continued on page 50)

MEDICAL NEWS *in brief*

(Continued from page 47)

as from the United Kingdom, participate annually in this school, which has become an international conference for the pooling of experience and discussion of health education problems. The inclusive fee for tuition and residence is £22.

Further particulars can be obtained from the Medical Director, The Central Council for Health Education, Tavistock House, Tavistock Square, London, W.C.1, England.

CATHOLIC HOSPITAL ASSOCIATION

The Catholic Hospital Association of the U.S. and Canada will hold its 43rd annual convention at Atlantic City, N.J., June 22-26.

The theme of this year's convention will be "The Hospital Apostolate in a Changing Era". Representatives from the 1200 Catholic hospitals in the U.S. and Canada, and several from foreign countries, will attend. Among the featured speakers for the sessions will be Dr. Lillian Moller Gilbreth, famous woman engineer and author of the best-seller "Cheaper by the Dozen"; and Danny Thomas, TV comedian, who will address the dinner for Religious on Tuesday, June 24. More than 5000 hospital administrators and employees attend the Catholic Hospital Convention each year.

THERAPEUTIC TRIAL OF AZACYCLONOL

Favourable clinical responses to azacyclonol (Frenquel) in various psychotic states have been reported. The best results were obtained in toxic hallucinatory states, whereas the results in schizophrenia have been variable. Gray and Forrest (*Brit. M. J.*, 1: 374, 1958) report results of treatment with azacyclonol in 56 patients with schizophrenia and two patients with alcoholic hallucinatory states.

Forty patients (20 men and 20 women) were subjects of a controlled trial; the mean age of the women was 51 and that of the men was 38; the mean length of the stay in hospital was 10 years. Their routine medication was maintained if it was considered that the patients' mental condition had remained stable for the four weeks preceding onset of the trial course of the new drug. The dose of azacyclonol was 60 mg. daily. The trial lasted 10 weeks and was so arranged that it was possible to compare changes in clinical rating during 30 "azacyclonol" periods and 30 "placebo" periods in the 40 patients.

Fourteen of the 30 patients showed improvement while receiving placebo; ten of the 30 patients improved on azacyclonol), four improved on azacyclonol alone, and six improved who were on additional drugs). Of three patients who had visual hallucinations, two claimed these stopped entirely. Every patient had auditory hallucinations; there was a diminution in intensity and frequency in some patients, yet in none did the experience cease altogether. There were some obvious changes in activity in men; they were more talkative and restless, and one was rated

worse because of obvious disturbances in thinking and perception.

In the clinical trial 18 patients were treated with azacyclonol in periods of from four weeks to three months. The dose varied from 60 to 180 mg. daily. The mean age of the group was 30, with a mean hospital stay of 18 months. The diagnoses were schizophrenia (16 patients) and alcoholic hallucinatory states (2 patients). Thirteen patients improved and six left the hospital. In eight patients the hallucinatory experience diminished and in four it stopped completely.

Evaluation of new drugs in psychiatry is difficult because chronic schizophrenics improve as a result of the additional attention involved in any therapeutic trial. Psychiatric assessment when applied to minor degrees of change in mental state is not very precise.

Azacyclonol seems to have no sedative effect, in fact appears to act partly as a cerebral stimulant. "Turbulence", used to describe restless activity, has been reported as a side effect. The apparent superiority of the placebo to the drug is due to the stimulating effect of the drug which made the patient's mental disturbance more obvious in the interview situation. The authors conclude that azacyclonol is unlikely to be a very useful drug in the treatment of chronic schizophrenia but they suggest that hallucinatory experience of recent onset, whether schizophrenic or toxic, is an indication for treatment with azacyclonol.

The only toxic effect observed was a rise of blood urea nitrogen in two patients out of a group of four who were subjected to detailed study. In one patient the elevation was not of significant degree, and in the other patient evidence of chronic nephritis was later established.

AWARDS FOR EXPERIMENTAL RESEARCH IN PROBLEMS OF AGING

The Trustees of the Ciba Foundation for the Promotion of International Co-operation in Medical and Chemical Research invite candidates to submit papers descriptive of work relevant to basic problems of aging, for the fifth and final annual awards for 1959.

Not less than five awards, of an average value of £300 each, are available for 1959. Announcement of awards will be made in August 1959. All entries must be received *not later than January 10, 1959.* The entries will be judged by an international panel of distinguished scientists including Prof. C. H. Best (Toronto). They will advise the Executive Council of the Foundation on their findings and will also have power to recommend variation in the size and number of the awards according to the standard of entries. The decisions of the Executive Council will be final. In making the awards preference will be given to younger workers. The papers may be in the candidate's own language, and should not exceed 7000 words in length. In all cases a summary in English, not exceeding in words 3% of the length of the paper, must be attached. If possible, 10

(Continued on page 52)

MEDICAL NEWS *in brief*

(Continued from page 51)

copies of reprints in English should be provided.

All entries should be sent to: Dr. G. E. W. Wolstenholme, Director and Secretary to the Executive Council, 41 Portland Place, London, W.1, England.

SURGICAL MANAGEMENT OF GIANT CAVITARY TUBERCULOSIS

In a series of 30 patients with giant cavitary tuberculosis (cavities of 4 cm. in diameter or more) treated with various combinations of chemotherapy and surgical measures, no permanent arrests of disease were obtained by Bell (*Am. Rev. Tuberc.*, 77: 593, 1958) in eight patients when Monaldi drainage alone was used. In the remaining 22 patients thoracoplasty or resection with or without preliminary Monaldi drainage was satisfactory in seven (one-third) of the group. Bell believes that the results are indicative of the advanced stage of the disease and of the type of patients with the disease rather than a reflection of the surgical method.

The most consistent treatment results were obtained by thoracoplasty, with disease arrest rates approaching 75% in the prechemotherapy period. Thoracoplasty failure or late relapse after intervals of five to ten years, however, averaged 10%. The advantages and safety of pulmonary resection when effective antituberculous drug coverage is available should make this the treatment of choice. Proceeding on the assumption that giant cavitary tuberculosis will be a therapeutic failure on nonsurgical treatment, the writer considers that early pulmonary resection should yield results similar to those for all varieties of cavitary tuberculosis.

CARBUTAMIDE IN TREATMENT OF SCHIZOPHRENIA

Carbutamide (BZ 55), appearing to act as a euphorizing antihallucinogen, has given encouraging results in the treatment of 60 patients with schizophrenic illness, 45 of whom left hospital recovered or relieved, according to Frost (*Brit. M. J.*, 1: 381, 1958).

The patients were given carbutamide 1.5 g. daily for not more than three successive days a week, followed by a drug-free interval of four days. They were encouraged to take glucose freely so that the hypoglycæmic effect of carbutamide was avoided during treatment. Two groups of cases were covered. The first consisted of new cases treated by carbutamide alone (30 cases) and the second consisted of 30 patients treated by deep insulin coma or by electroconvulsive therapy at some time in the past before carbutamide was used. In the first group, made up of recent cases with shorter histories, 26 patients were alleviated; in the second, 19 improved.

The results from the diagnostic classification showed that of seven teen-age hebephrenes, five did well on carbutamide; of eight cases of mental defect or mental retardation

with superimposed schizophrenia, all, defective and retarded, went home relieved; of 11 paranoid persons, four recovered, four were relieved and three were not improved; of the 15 schizo-affective cases eight recovered, four were relieved and three were not improved; of six cases with obsessive features, three were relieved and three not improved.

The author states that carbutamide renders paranoid schizophrenics accessible to psychotherapy in a state of clear consciousness untrammelled by hallucinosis, depression or thought blocking.

Counts of white cells and thrombocytes and liver function tests were made routinely. In this series no death occurred, there was no leukopenia, and in only two cases was there a temporary drop in the leukocyte count. Bone-marrow soup was given daily as a prophylactic against agranulocytosis.

—

VALUE OF AMINOPYRINE

Six cases are reported by Cardon *et al.* (*Ann. Int. Med.*, 48: 616, 1958) to illustrate the potent antipyretic effect of aminopyrine. In three of these cases — one of periarteritis nodosa and two of exacerbation of rheumatic fever— aminopyrine was the only drug which controlled the fever and reversed the progressive downhill course of the disease, after weeks of ineffective therapy with large doses of chemotherapeutic and antibiotic agents. In these three cases the action of aminopyrine simulated that of a specific drug and proved to be life-saving. Agranulocytosis did not occur even in the cases where the drug was given over long periods of time, and a tendency to leukopenia in one case was readily controlled by reduction in dosage. Aminopyrine is considered to be of value particularly in conditions not amenable to therapy with specific chemotherapeutic and antibiotic agents, or where these prove to be ineffective; in cases where other antipyretics are not tolerated or have failed; and in cases where one is unwilling to assume the risks of therapy with corticotrophin and the corticosteroids, or these have failed, or some specific contraindication to their use exists. However, aminopyrine may be used in any condition as the primary agent to control high or prolonged fever, alone, or as a supplement to other therapy.

The authors conclude that aminopyrine is still a uniquely valuable and occasionally life-saving antipyretic which deserves a trial whenever fever is a significant feature of the clinical picture of disease. It may be effective under conditions in which other antipyretics and even the most powerful and specific of the newer drugs fail. They consider that the danger of granulocytopenia from its use, although real, has been overemphasized and is no greater than with many other drugs in common use today. Aminopyrine has its place in therapeutics under well controlled clinical conditions and under the supervision of a physician, but its careless and indiscriminate use is to be condemned.

(Continued on page 54)

MEDICAL NEWS *in brief*

(Continued from page 53)

CAVAL-PULMONARY ANASTOMOSIS FOR VASCULARIZATION OF THE LUNG

An experimental method is described by Robicsek *et al.* (*J. Thoracic Surg.*, 35: 440, 1958) for the relief of certain congenital heart diseases associated with impaired pulmonary circulation. The essence of the procedure is as follows: the superior vena cava is transsected before entering the right atrium; the right pulmonary artery is severed at its origin with the main pulmonary trunk; the peripheral stumps of the two vessels are anastomosed by an end-to-end method. The right lung is thus supplied with blood directly from the superior vena cava. In this manner, about half of the systemic venous blood flow by-passes the right heart.

Animal experiments have indicated that pulmonary blood flow and oxygen uptake are nearly equal on both sides. There is no significant increase in blood pressure in the area of the superior vena cava. The method as illustrated is considered to have advantages over other anastomotic operations in the following respects: (1) the operation places no extra burden on the heart; (2) blood pressure in the main trunk of the pulmonary artery is not increased; (3) this anastomosis supplies "pure" venous blood to the lung; (4) endarteritis is less likely to occur; and (5) technically the operation, even on small subjects, is not difficult.

Detailed physiologic changes, hæmodynamics, and angiocardiography studies are reported.

STIMULATION OF BRONCHIAL SECRETIONS IN HUMAN SUBJECTS

Bickerman *et al.* (*Dis. Chest*, 33: 347, 1958) report a method of obtaining sputum from the respiratory tract of normal persons, patients with chronic nontuberculous pulmonary disease, and patients with known or suspected malignancy. The basis of this procedure involves the inhalation of warm, hygroscopic saline aerosols. Approximately 10 c.c. of a 10 or 15% saline aerosol containing 20% propylene glycol was administered to a total of 336 subjects. Mucoid sputum specimens suitable for cytologic examination were recovered in 88.5% of the series who had no evidence of pulmonary disease and no cough or spontaneous sputum. Sputum was produced in 86% of 180 subjects who had no evidence of pulmonary disease, and no cough or spontaneous sputum. Only three subjects in this group noted a slight irritation on inhaling the warm 10% saline aerosol.

Cytologic studies of the sputum recovered from 74 subjects following the inhalation of 10% saline showed that 79% of the specimens were satisfactory for diagnosis. In five of the eight patients with documented primary or metastatic carcinoma in the lung, sputum preparations were positive for malignant cells. There were no false negative reports. Since all of the

examinations were performed on single specimens, it is evident that cytologic study of repeated specimens obtained in a similar manner might increase the possibilities of accurate diagnosis. The authors claim that the method of inducing sputum may be expected to demonstrate tumour cells from symptomless individuals before spontaneous sputum arises, since the specimens obtained by hypertonic saline aerosol are entirely adequate for study. Inhalation of nebulized 20% propylene glycol at a temperature of 120° F. was also employed to facilitate expectoration of retained secretions in patients with bronchopulmonary disease. The authors feel that this may constitute a possible screening technique for the cytologic diagnosis of lung cancer.

THE "UNEXPLAINED" HIGH ERYTHROCYTE SEDIMENTATION RATE

An unexplained rise of the sedimentation rate above 20 mm. in one hour was found by Ansell and Bywaters (*Brit. M. J.*, 1: 372, 1958) in 51 new patients out of approximately 900 attending a rheumatology clinic over a period of 3½ years. Thirty-one of these remained high over one month. In this group 15 of the patients were over 60 years, 10 in their sixth decade and six under 50.

Since a raised E.S.R. may be the only sign of serious disease, further investigations, including electrophoresis of the serum for protein pattern, differential agglutination titre (D.A.T.), search for C-reactive protein and L.E. cells, fibrinogen estimation, and determination of antistreptolysin titre and of serum uric acid level, were made. In certain cases biopsies of the bone marrow or of synovial membrane were obtained.

A final diagnosis of rheumatoid arthritis was made in patients with polyarthritis (1) with a positive D.A.T., or (2) with erosions on x-ray films, or (3) with low viscosity high-protein-containing synovial fluid without infection. The final diagnosis of probable rheumatoid arthritis was made in patients with neither a positive D.A.T. nor x-ray erosions, but in whom pain, swelling, and limitation were present in multiple joints over a period of at least six months, without evidence of other conditions to cause this.

Eight of the 31 patients with a high E.S.R. developed typical rheumatoid arthritis, while six were probably suffering from this disorder.

The high incidence of rheumatoid arthritis in patients of advancing years and the difficulty in establishing its diagnosis are of particular interest. In this group other diseases found were tuberculosis of the knee joint, myelomatosis, bronchial carcinoma, phlebothrombosis (two cases), and presence of cold agglutinins. In 11 patients no cause was found for the high E.S.R. and their general health has remained good. In five the E.S.R. returned to normal in one year, and in six it has remained high.

The presence of a high E.S.R. should lead to a careful assess-

(Continued on page 56)

MEDICAL NEWS *in brief*

(Continued from page 55)

ment and investigation of the patient, but, particularly in older people, it is not necessarily associated with a bad prognosis.

PREOPERATIVE BRONCHIAL BIOPSY IN PULMONARY TUBERCULOSIS

At the Ohio Tuberculosis Hospital, biopsy of the lobar bronchus draining an area of active tuberculous disease was carried out before operation. Surgical resection of the affected area was then performed, and the findings correlated with the results of bronchial biopsy and of simple gross bronchoscopic observations.

In this series of 100 patients, reported at the annual meeting of the American Trudeau Society in Philadelphia, it was shown that the bronchoscopic appearance of the mucosa does not reflect the condition of the bronchus; only by biopsy can the presence of submucosal inflammation be ascertained. The biopsy gave rise to no complications.

PREGNANCY AFTER THORACIC SURGERY FOR TUBERCULOSIS

The following conclusions are drawn by Schaefer and his colleagues of New York after studying 29 patients who gave birth to 32 infants after major thoracic operations for tuberculosis before or during pregnancy: (1) Pregnancy may be safely undertaken after major thoracic surgery for tuberculosis if medical and obstetrical care are adequate. (2) Thoracic surgery may be undertaken during the first and second trimesters of pregnancy. (3) Pregnant patients should receive antimicrobial therapy before, during and after pregnancy in the same way as the non-pregnant woman. (4) These patients do not suffer commonly from respiratory embarrassment in pregnancy or labour. These conclusions were reported at the annual meeting of the American Trudeau Society in Philadelphia in May.

STEROIDS AND SARCOIDOSIS

At the Mount Sinai Hospital, New York, 37 patients with sarcoidosis have been treated with prednisone and prednisolone in the last three years. This represents about 30% of all patients with sarcoidosis. Results were similar to those obtained with cortisone in previous years, but the newer steroids were easier to administer. Only one case of tuberculosis developed among a total of 58 patients receiving steroids; however, all patients with intrathoracic sarcoidosis are now given 300 mg. of isoniazid daily as well as the steroid.

The steroid proved more effective with fresh lesions than with older ones; it suppressed fever, cough, dyspnœa, hypercalcæmia, and hyperglobulinæmia. Marked clear-

ing occurred in lung lesions, peripheral lymph nodes and ocular lesions. Mediastinal lymph nodes and enlargement of liver or spleen were less responsive. Skin lesions responded to therapy but recurred when the drugs were stopped. Steroid therapy did not cure the patients, but proved beneficial in suppressing the disease when its unremitting course was producing loss of organ function or even threatened life. Maintenance dosage of prednisone and prednisolone was usually 7.5 to 15 mg.—American Trudeau Society Meeting, Philadelphia, May 1958.

NEW JOURNAL ON SPORTS MEDICINE

The Association of Austrian Sport Physicians has begun publication of its official organ, *Sportärztliche Praxis* (The Practice of Sport Medicine). The first issue begins with a posthumous article by Dr. Felix Mandl and continues with contributions on various injuries associated with sports, including a contribution showing the preponderance of left-sided injuries in skiing. There are also articles on sport education, and abstracts and book reviews. The journal will be published quarterly by the Verlag Brüder Hollinek, Wien 3, Steingasse 25.

AMERICAN HEART ASSOCIATION

The American Heart Association will hold its annual scientific sessions in San Francisco, October 24-26. Items tentatively scheduled for the program include a session on genetics, presented jointly by the Heart Association and the American Society for the Study of Arteriosclerosis, which is holding its annual meeting at the same time as the A.H.A. There will be an evening session on instrumental study of the heart and circulation, and an all-day session for physicians in general practice and for internists. The Lewis A. Conner Memorial Lecture will be given by Dr. John H. Gibbon of Philadelphia on "The Maintenance of Cardio-Respiratory Functions by Extra-corporeal Circulation", and the George E. Brown Memorial Lecture by Dr. Lewis Thomas of New York on "The Role of Hypersensitivity in Cardiovascular Disease".

CANADIAN ARTHRITIS AND RHEUMATISM SOCIETY

The 1957 Annual Report of the Canadian Arthritis and Rheumatism Society shows a growth in volume of the Society's activities in 1957; 8156 patients were treated in this year as compared with 7486 in 1956. Advances were also made in research and professional education. In his report, the national president, Mr. B. H. Rieger, mentions three problems facing the Society: "First there is the problem of more rapid extension of its services into small towns and rural areas. The lower density of population and lessened ade-

(Continued on page 58)

MEDICAL NEWS *in brief*

(Continued from page 57)

quacy of other community health and welfare resources encountered in such communities tend to raise the Society's unit and total costs to a level beyond their unaided economic resources.

"The second problem is that of financing an expanding program of medical research. Intellectually self-generating medical research flourishes only in the presence of assured financial support which provides dollar growth at a rate which keeps pace with scientific growth.

"Finally, there is the need to increase special facilities for the care of in-patients. The Society perceives a great need for the establishment of regional special treatment centres at or in conjunction with selected general hospitals as a feature of coming hospitalization insurance schemes. In part, the solution of these problems lies in increased financial support through voluntary contribution and through government grants."

NEW YORK COURSES IN DERMATOLOGY

The New York University-Bellevue Medical Center Post-Graduate Medical School offers the following courses by the Department of Dermatology and Syphilology, under the direction of Dr. Marion B. Sulzberger.

Comprehensive review in dermatologic histopathology: A full-time intensive course, September 8-12, 1958, with a complete review of both the normal histology of the skin and the essential histopathology of diseases of the skin.

Dermatology and syphilology (for pædiatricians): An intensive full-time review course, October 6-10, 1958, including clinical sessions and demonstrations of patients together with the application of modern diagnostic and therapeutic modalities, illustrations of common and rare skin diseases, and illustrated lectures covering differential diagnosis, causes, and newest forms of treatment.

Seminar in dermatology and syphilology (for general physicians): A full-time intensive course, February 16-20, 1959, with illustrated lectures and demonstrations of patients and methods.

Symposium on dermatology and syphilology (for dermatologists): A full-time course, May 18-22, 1959, consisting of a survey and critical evaluation of recent advances and research in dermatology and syphilology. Demonstration of patients and application of new techniques are included.

For further information, write to: Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

COMMONWEALTH CHEST CONFERENCE

The Commonwealth Chest Conference will be held in the Royal Festival Hall, London, England, July 1-4. This series of lectures, discussions and clinical meetings will be followed by three days (July 5, 6 and 7) devoted to visits to hospitals, clinics and rehabilitation centres. On Tuesday, July 1, the Section meetings of the National Association for the Prevention of Tuberculosis will be held, and the next two days will include a number of symposia on various aspects of chest disease.

Apart from themes in tuberculosis, the following will be discussed—Respiratory Disease, A Malady of Environment; Management of the Heart in Chronic Respiratory Disease; The Heart Patient in Everyday Life; Fungus Disease of the Lung; The Patient's Personality; The Problem of Lung Cancer. Further information from: The National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1, England.

—

TRANQUILLIZING DRUGS AND PATIENTS IN MENTAL HOSPITALS

Brill and Patton (*Am. J. Psychiat.*, 114: 509, 1958) have studied the fall in the number of patients in mental hospitals in New York State. At the end of 1955-56, the residual population in mental hospitals showed a fall of 500 patients in comparison with the increase of 2500 of the year before and the average rise of 2000 per year for the previous decade. It is concluded that this fall is to a great extent due to the extensive use of tranquillizing drugs, of which chlorpromazine now constitutes about 75%. Mental hospital admissions are still high in New York State, but patients remain for a shorter time. In addition there is a marked decrease in the need for restraint of violent patients.

Obviously the evidence presented does not constitute absolute proof of the efficacy of tranquillizers, but it is nevertheless strong evidence. However, the authors also mention that there was a fall in the mental hospital population during World War II.

—

"DIRECT ANALYSIS" IN THE TREATMENT OF SCHIZOPHRENIA

In 1947 Dr. John Rosen treated 37 cases of what he termed "deteriorated schizophrenia" by conversing with patients in the language of the unconscious and being in a position to interpret the unconscious to the patients at every available opportunity. This time-consuming technique was claimed to have led to recovery of all of the patients and to the achievement of such a degree of integrity of the personality and of emotional stability that they were able to live comfortably outside an institution and to withstand at least as much environmental assault as is expected of a normal person who has not experienced a psychotic episode.

Ten years later, Horowitz *et al.* (*Am. J. Psychiat.*, 114: 780, 1958) were able to identify 19 of the original group of 37 patients. (It had been reported in 1952 that six were psychotic and probably institutionalized.) These patients

(Continued on page 60)

MEDICAL NEWS *in brief*
(Continued from page 59)

were subjected to follow-up investigation which consisted of interviews of themselves and of their nearest relatives when possible. This afforded an opportunity of revising the original diagnosis and it was noted that six of these 19 patients were psychoneurotic and one was a manic depressive. This left only 12 patients correctly diagnosed as schizophrenic, nine of whom have had from two to five admissions to mental hospitals during the past ten years; two have undergone psychosurgery and one has continued to have symptoms sufficiently severe to have requested additional psychosurgical evaluation. Obviously direct-analytic therapy had not produced any lasting results in any one of them. "Whatever the merits of direct analytic therapy for schizophrenia, the claim that it results in a high degree of recovery remains unproven."

—

INHALATION OF HAIR SPRAY MIXTURES

Attention has recently been drawn by Bergmann, Flance and Blumenthal in the *New England Journal of Medicine* (258: 471, 1958) to the danger of inhaling hair spray solutions. These preparations, usually dispensed as Freon "bombs", contain synthetic or naturally occurring resins in solution. These inert substances cannot be metabolized by the body and molecules of sizes up to 20,000 will pass through the glomeruli in the urine. Molecules up to 70,000 of molecular weight pass much less readily through the kidneys. The larger particles, which may be up to 1,000,000 of molecular weight, are phagocytized in the reticulo-endothelial system and produce granulomatous reactions. Such lesions in the lymph nodes may superficially resemble sarcoidosis.

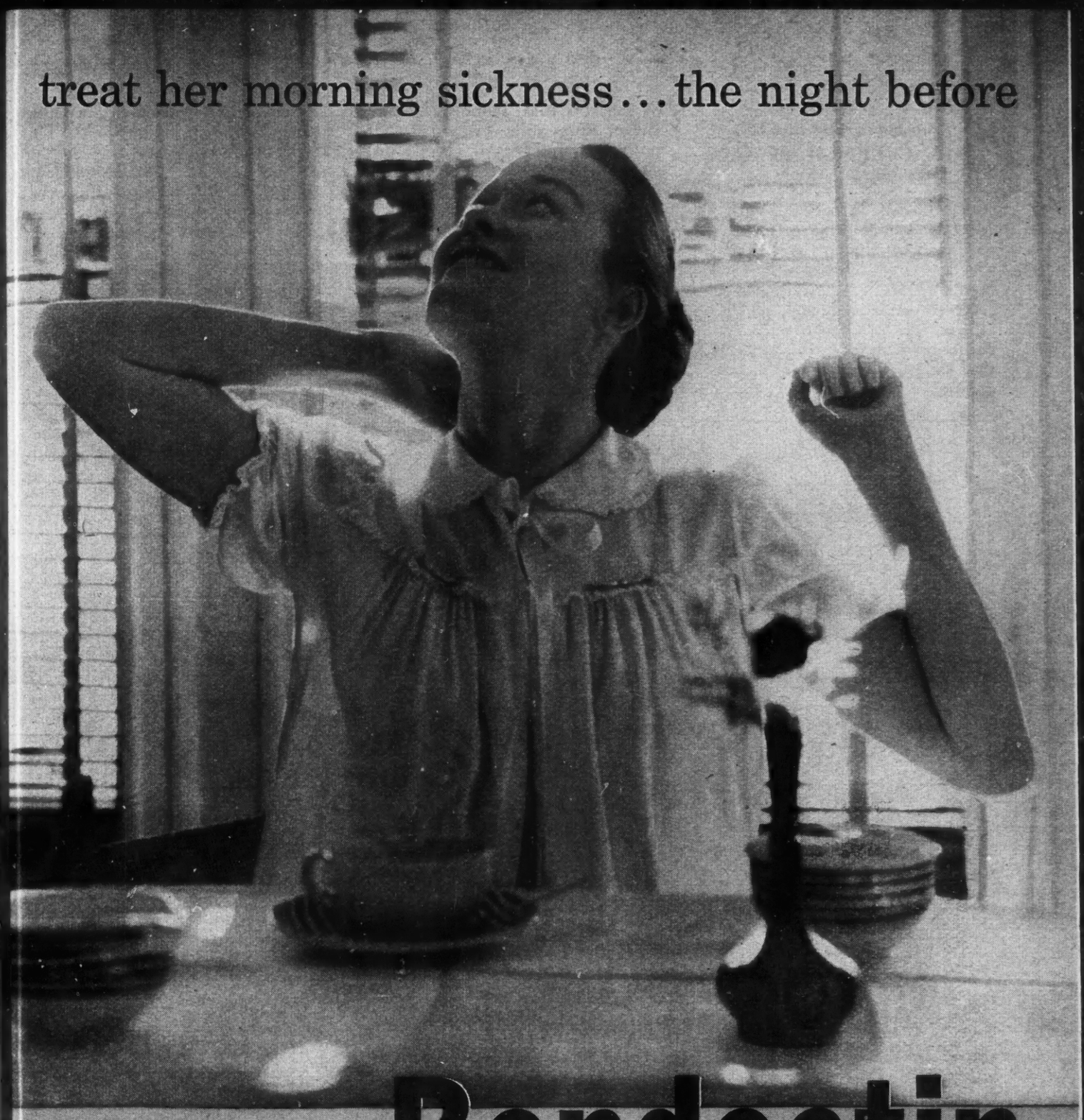
The authors have reproduced these lesions in guinea-pigs by injecting the animals with a concentrate of these commercial products. A granulomatous inflammation was produced at the site of injection and the presence of a typical micromolecular substance was demonstrable in the reticulo-endothelial cells of the liver and spleen. In some of these animals the lung showed a very intensive inflammatory reaction. Improvement in the radiological appearance of the lungs in the two patients seen with this form of thesaurosis may have been due to the transport of the foreign material from the lungs to the liver for indefinite storage or to a subsidence of the inflammatory reaction as the foreign material was slowly metabolized.

—

DIAGNOSTIC SIGNIFICANCE OF BLEEDING FROM THE LUNGS

In cases of hæmoptysis with a negative chest radiograph one should think of bronchiectasis, mitral stenosis and bronchial adenoma. Angiomata are particularly prone to bleed, and a foreign body must be excluded even in the absence of a history of aspiration. Congenital cysts secondarily infected with Aspergillus can be the cause of recurrent hæmoptysis over a period of years and can easily escape recognition unless tomograms are done.—A. Brunner: *Deutsche med. Wchnschr.*, 83: 237, 1958.

(Continued on page 62)



treat her morning sickness... the night before

in 941 cases[1,2] Bendectin effective in all but 17

2 tabs. h. s.

Merrell
SINCE 1828

THE WM. S. MERRELL COMPANY
New York • ST. THOMAS, ONTARIO • Cincinnati
Another Exclusive Product of Original Merrell Research

1. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.
2. Clinical communications, 1956-57.

TRADEMARK: "BENDECTIN"

MEDICAL NEWS *in brief*

(Continued from page 60)

LOW CEREBRAL SPINAL FLUID PRESSURE

A series of 32 patients with low cerebral spinal fluid pressure was reviewed by Shenkin and Finneson (*Neurology*, 8: 157, 1958). The lower limit of normal was considered for C.S.F. pressure to be 70 mm. of water in the lateral recumbent position with the head at the same level as the vertebral column. Considering the anatomy of the structure, namely the rigidity of the walls formed by the cranium, changes in C.S.F. pressure may merely reflect changes in volume of intracranial content. Dehydration or cachexia will reduce the fluid content of the brain and at the same time raise the osmolarity of the blood and therefore increase reabsorption of fluid. These disease states will therefore result in a lowering of C.S.F. pressure.

The headache encountered after a lumbar puncture is presumed to be caused by leakage of fluid through the puncture hole. This theory, however, has never been proven and is challenged by another one which claims that injury to the meninges may set up a localized reflex vasospasm of the choroidal vessels which would bring about a decrease in C.S.F. production. Be it as it may, headache alleviated by the supine position and exacerbated by the upright position has been encountered in patients with low C.S.F. pressure of unknown etiology. These cases of spontaneous intracranial hypotension were usually characterized also by vomiting, rigidity of the neck and photophobia. In some, carbon dioxide inhalations seem to act as a specific therapy by presumably causing vasodilatation of the intracranial vessels and therefore probably increasing cerebrospinal fluid production.

It must be noted that hyperventilation reduces C.S.F. pressure and may therefore contribute to the vertiginous state which it brings about. In general it can be stated that changes in cerebral blood flow always induce changes in C.S.F. pressure in the same direction.

Certain cases of arteriosclerosis with decreased cerebral blood flow show reduced C.S.F. pressure, which may reflect the reduction in size of the intracranial vascular bed. The reduced intracranial circulation may also curtail C.S.F. production. A low C.S.F. pressure in cases of mental obtundity may be of value in ruling out an intracranial expanding lesion in favour of cerebral arteriosclerosis.

TUMOUR CELLS IN BLOOD IN BRONCHOGENIC CARCINOMA

Ross of Buffalo has studied the peripheral blood in cases of proven bronchogenic carcinoma and found that 15% of patients admitted with this disease had tumour cells in preparations made from peripheral venous blood. In blood samples from the pulmonary vein taken at operation, 70% of specimens showed tumour cells after operative manipulation. One week after resection, no tumour cells could be found in any specimen from a peripheral vein. These findings were reported at the annual meeting of the American Trudeau Association in Philadelphia.

(Continued on page 64)

MEDICAL NEWS *in brief*

(Continued from page 62)

SIR GORDON GORDON-TAYLOR

The March issue of the *British Journal of Surgery* was a birthday number in honour of the eightieth birthday of that distinguished British surgeon, Sir Gordon Gordon-Taylor. Sir Gordon has been associated with the journal since its inception in 1913. He is no stranger to Canada, being an honorary Fellow of the Royal College of Surgeons of Canada and the possessor of an honorary doctorate from the University of Toronto. Many Canadians will wish to join in extending good wishes to this distinguished surgeon, historian, classical scholar and patriotic Scotsman.

FIRST CANADIAN KIDNEY TRANSPLANT

Strip cartoon addicts who follow the adventures of Rex Morgan, M.D., in their local paper will know that recently the problem of transplanting a kidney from one identical twin to another has been illustrated in his columns. This operation has been performed nine times in the United States, on seven occasions at the Peter Bent Brigham Hospital in Boston. In the middle of May, the Royal Victoria Hospital, Montreal, had the honour of being the first hospital in Canada at which an apparently successful transplant of a healthy kidney from a 16-year-old girl to her identical twin sister was carried out.

Before operation, tests were carried out to prove that the girls were identical twins; these included studying healing of a sample skin graft from one to the other, and careful blood grouping. At operation, one surgeon prepared the recipient to receive the new kidney, while in an adjacent operating room another surgeon performed a nephrectomy on the donor. The two then cooperated on the grafting operation and within 20 minutes the transplanted kidney had begun to function satisfactorily.

Legal aspects of the operation had to be considered, since it involved removal of an important organ from a healthy person. A family council was therefore

(Continued on page 67)

MEDICAL NEWS *in brief*

(Continued from page 64)

called, and a special court order obtained, before the authorities at the Royal Victoria Hospital felt that they could legally proceed with the operation.

—

ATHEROSCLEROSIS AND PHYSICAL ACTIVITY

Material from the Medical Examiner's Office in Westchester County, New York, relating to cases of coronary disease over a period of eight years was reported on at the American Trudeau Society meeting in Philadelphia in May. Cases in which death occurred from coronary occlusion, and cases in which apparently "normal" individuals died suddenly from accident, suicide or homicide were studied with a view to correlating the degree of coronary disease with occupational physical activity.

It was clearly shown that in white males, death from coronary artery disease occurs at a relatively younger age in those in sedentary occupations, though there is no difference as regards the degree of atherosclerosis found among "normal" individuals in different occupations. It would seem that physical activity promotes the development of collateral circulation, and that death at an earlier age in sedentary males is not related to acceleration of the atherosclerotic process but to an inadequate development of collateral circulation. Furthermore, sudden physical exertion was a negligible factor in deaths from coronary disease in the overwhelming majority of cases.

—

NEW THORACIC RESEARCH INSTITUTE IN STOCKHOLM

The new seven-storey Thoracic Research Institute and clinic building of the Carolinian Institute, presided over by Professor Clarence Crafoord, was inaugurated by King Gustaf Adolf of Sweden on May 9. The Institute has received a special grant of $200,000 from the Rockefeller Foundation for promoting scientific research at the clinic. Equipment includes the heart-lung machine developed by Professor Crafoord and his assistants in collaboration with the Swedish Aga Company and now industrially produced by the Aga Company. So far some 25 clinics in Sweden and abroad have been equipped with this machine.

There is also a special hibernation table designed by Professor Jack Adams-Ray of the Carolinian Institute for cardiac surgery under hyperthermia. — Swedish - International Press Bureau.

—

TRACHOMA MANUAL

The differential diagnosis and treatment of trachoma are discussed in "Trachoma Manual and Atlas", published by the Public Health Service, U.S. Department of Health, Education, and Welfare. Designed primarily for use in the Public Health Service's Indian health program, this 42-page illustrated manual is by Phillips Thygeson, clinical professor of ophthalmology at the University of California School of Medicine, San Francisco. Dr. Thygeson serves as consultant to the Division of Indian Health of the Public

(Continued on page 68)

MEDICAL NEWS *in brief*

(Continued from page 67)

Health Service on trachoma training and control programs.

Once prevalent among the general population in certain sections of the United States, trachoma rarely is found today except among Indians. The disease has persisted among the American Indians, occurring in acute and chronic form, despite intermittent control activities dating from the 1930's. A comprehensive survey of Indian health made after the transfer of the Indian health program to the Public Health Service from the Bureau of Indian Affairs in 1955 revealed a recrudescence of the disease which required development of a trachoma control program and preparation of a manual for training purposes.

"Trachoma Manual and Atlas" (Public Health Service Publication No. 541) is available from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., for 55 cents a copy.

PENICILLIN IN PEPTIC ULCER

According to Gordon and his colleagues from Moscow (*Klinicheskaya Meditsina*, 2: 22, 1958) penicillin is a valuable adjunct in the treatment of peptic ulcer with complications. In cases with marked inflammatory reaction surrounding the ulcer, penicillin therapy cleared the inflammatory œdema or decreased it considerably. This was of help in differentiating benign from malignant gastric ulceration. Biliary infection if associated with peptic ulcer is also an indication for penicillin therapy. The authors feel, however, that the question of efficacy of penicillin in healing peptic ulcers themselves has to be further studied; their results were inconclusive.

VERTEBRAL INTERSPACE INFECTIONS AFTER INTERVERTEBRAL DISC OPERATIONS

Postoperative infection of intervertebral spaces may be difficult to diagnose, because symptoms may not appear until several weeks after a disc operation or because of lack of objective signs such as fever and local manifestations. Eleven cases of such infection were recognized by Sullivan *et al.* (*J. A. M. A.*, 166: 1973, 1958) in a series of patients who had undergone surgical removal of a nucleus pulposus. Pain, which sometimes appeared within four to five days after operation, was delayed in others as long as 10 weeks. It was excruciating and in some resembled the original pain ascribed to protrusion of the lumbar disc. Radiation to the abdomen and groin resulted in a needless laparotomy in one case. In the course of a few weeks the process became visible in the roentgenograms and fusion was the outcome after six months to two years. The pain responded to adequate immobilization of the vertebral column by rigid brace or

(Continued on page 72)

MEDICAL NEWS *in brief*

(Continued from page 68)

plaster-of-Paris cast. In addition, antibiotics were given and in three cases the operative area was re-explored. Drainage resulted in dramatic relief in one case but did not help in the other two cases. The only positive laboratory sign present in most of these patients was an increase in erythrocyte sedimentation rate.

SYMPTOMATOLOGY AND OPERATIVE TREATMENT OF AORTIC STENOSIS

Significant clinical symptoms and hæmodynamic disturbances can be expected when the circumference of the aortic valve opening is reduced from its normal of 7.5 cm. to 2 cm., according to Derra, Kaiser and Loogen (*Deutsche med. Wchnschr.*, 83: 525, 1958). This reduces the opening area from 3 to 0.5 sq. cm. In mild stenosis the pressure gradient between the left ventricle and the aorta need not be above 20-40 mm. Hg, but in severe forms it can rise to 40-100 and more. For purposes of evaluation of operative therapy, four degrees of severity are distinguished: (1) asymptomatic – pressure gradient, 0-40 mm. Hg; (2) moderate symptoms—pressure gradient, 40-80 mm. Hg; (3) angina pectoris and syncope—pressure gradient, generally over 80 mm. Hg; (4) severe forms with obvious left ventricular failure and often with failure of the right ventricle as well. The first group does not require operation, the second group is at the ideal stage for operation, and in the third group operation is urgently necessary if the symptoms are due to aortic stenosis. In the fourth stage, operation may be the only thing left to offer the patient but its outcome is most uncertain because of the poor condition of the patient and because the stenosed valves are often too calcified to permit operative sectioning.

Twenty-four patients, 20 males and 4 females, aged 6-47, underwent operation by the transventricular approach. Results were good in 13, moderate in 4, and unsatisfactory in 2; there were 5 postoperative deaths. In 5 cases it was impossible to relieve the stenosis; they include 3 of the fatalities.